Mechanical Ventilation: Essentials for Current Adult and Pediatric Practice

Editors:
Ira Cheifetz, MD, FCCM
Neil MacIntyre, MD
John J. Marini, MD
ABIM, board membership; ATS, AARC, committees; Daedalus, Editor

Kathryn Hibbert, MD
Massachusetts General Hospital
Boston, Massachusetts, USA
No disclosures

Sameer Kamath, MD
University of Iowa
Iowa City, Iowa, USA
No disclosures

Martin C.J. Kneyber, MD, PhD, FCCM
Pediatric Intensivist
Chief, Division of Critical Care Medicine
Beatrix Children's Hospital
Groningen, Netherlands
ESPNIC

James W. Leatherman, MD
Director MICU
Hennepin County Medical Center
Minneapolis, Minnesota, USA
ABIM Critical Care board member

Sean Levy, MD
Graduate Assistant
Division of Pulmonary and Critical Care Medicine
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts, USA
No disclosures

Philip Lumb, MB, BS, MD, MCCM
Professor and Chairman
LAC and USC Medical Center
Los Angeles, California, USA
Levosimendan Investigator/Tenax Corporation
Committee Chair for: Committee for Health Systems Improvement and Center of Health Systems Innovation

Christopher Newth, MD, FRCPC
PICU Administration
Children's Hospital of Los Angeles
Los Angeles, California, USA
Philips Healthcare, consulting on monitoring devices in pediatric ICU; Covidien, consulting on endotracheal tubes for infants and children

Donald Null Jr, MD
Medical Director NICU
UC Davis Children's Hospital
Sacramento, California, USA
Mallinckrodt, Speakers Bureau; Drager, consultant; Perussionaire, ventilators supplied for research

Gisele Padilha
Postdoctorate in Physiology
Laboratory of Pulmonary Investigation
Carlos Chagas Filho Biophysics Institute
Federal University of Rio de Janeiro, Brazil
No disclosures

Paolo Pelosi, MD
Istituto Di Anestesia E Rianimazione
Ospedale Policlinico
Parthak Prodhan, MD, FCCM  
Arkansas Children’s Hospital  
Little Rock, Arkansas, USA  
PC4; SPR, participating member

Adrienne Randolph, MD, MS  
Professor of Anaesthesia and Pediatrics  
Boston Children’s Hospital  
Boston, Massachusetts, USA  
Section editor for pediatric critical care medicine for UpToDate. Research grant recipient, Genentech, Inc.  
ATS (co-leader of pediatric critical care medicine working group), International Sepsis Forum (Council Member), SCCM Peds Critical Care Section member

Courtney M. Rowan, MD  
Pediatric Critical Care  
Riley Hospital for Children  
Indianapolis, Indiana, USA  
Foundation research grant recipient

Bruce K. Rubin, MEng, MD, MBA, FRCPC  
Professor and Chair, Department of Pediatrics  
Virginia Commonwealth University School of Medicine  
Richmond, Virginia, USA  
Patenten licensed to InspiRx; Funding from the CF Foundation, The Denny Hamlin Foundation; Trustee ARCF, Board, March of Dimes

Gregory A. Schmidt, MD  
Professor of Medicine  
University of Iowa  
Iowa City, Iowa, USA  
ACCP: Faculty in mechanical ventilation course; ATS/ACCP Co-chair, mechanical ventilation guidelines committee

Craig A. Schramm, MD  
Connecticut Children’s Medical Center  
Hartford, Connecticut, USA  
Member - Pediatric Chest Medicine Network Steering Committee, American College of Chest Physicians

J. Brady Scott, MS, RRT-ACCS, FAARC  
Director of Clinical Education  
College of Health Sciences Rush University  
Chicago, Illinois, USA  
Aerogen-Key Opinion Leader; Sunovion Pharmaceuticals, advisory board member; American Association for Respiratory Care; speaker at national conference, webinar presenter; American College of Chest Physicians, Faculty, Mechanical Ventilation course

Robert Shapiro, MD  
Staff Physician  
Hennepin County Medical Center  
Minneapolis, Minnesota, USA  
No disclosures

Shihab Suageir, MD  
Pasadena, California, USA  
ASA and CSA Member

Robert F. Tamburro, MD, MSc  
Pennsylvania State Children’s Hospital  
Hershey, Pennsylvania, USA  
US FDA Office of Orphan Product Development Grant, Ony, Inc. Springer Publisher royalties for serving

**David A. Turner, MD**
Associate Director,
Graduate Medical Education
Duke University Hospital and Health System
Associate Professor
Director of Pediatric Critical Care
Department of Pediatrics
Duke Children’s Hospital
Durham, North Carolina, USA
CHEST; fellow

**David L. Vines, MHS, RRT, FAARC**
Rush University
Chicago, Illinois, USA
Halyard Health - research grant; Aerogen Ltd- research grant; Teleflex Medical - advisory board, speaking; Medtronic- consulting; Bayer Healthcare Pharmaceuticals, Inc and Boehringer Ingelheim Pharmaceuticals, Inc - Medical advisory boards; National Board for Respiratory Care- board member; Chest- Speaker; AARC- speaker

**Duane C. Williams, MD**
North Chesterfield, Virginia, USA
No disclosures
Contents

Chapter 1: Clinical Design Features of Modern Mechanical Ventilators
Neil MacIntyre, MD

Chapter 2: The Concept of Lung Protective Ventilation/Managing Acute Lung Injury and Parenchymal Lung Disease in Adult and Pediatric Patients
Sean Levy, MD, Ira Cheifetz, MD, Kathryn Hibbert, MD

Chapter 3: Cardiopulmonary Interactions
John Marini, MD, and Parthak Prodhan, MD, FCCM

Chapter 4: Optimizing Patient-Ventilator Synchrony in Adult and Pediatric Populations
John D. Davies, MA, RRT, and Martin C. Kneyber, MD, PhD, FCCM

Chapter 5: Managing Obstructive Lung Disease in the Adult
James W. Leatherman, MD, and Robert Shapiro, MD

Chapter 6: Mechanical Ventilation in Pediatric Obstructive Lung Disease
Duane C. Williams, MD, and Bruce K. Rubin, MEng, MD, MBA, FRCPC

Chapter 7: Disease-Specific Strategies for Mechanical Ventilation of Newborns
Donald Null Jr, MD

Chapter 8: Managing Ventilator Support of Normal Lungs in Adult and Pediatric Patients
Anoopindar Bhalla, MD, Christopher Newth, MD, FRCPC, Paolo Pelosi, MD, Marcelo Gama de Abreu, MD, Gisele Padilha, and Lorenzo Ball, MD

Chapter 9: Strategies for Ventilator Discontinuance
Dean Hess, RRT, PhD, FCCM, and Adrienne Randolph, MD, MS

Chapter 10: The Role of Rescue Treatments for ARDS
Courtney M. Rowan, MD, Shira J. Gertz, MD, Robert F. Tamburro, MD, MSc, and Gregory A. Schmidt, MD

Chapter 11: Noninvasive Ventilation in the Adult
J. Brady Scott, MS, RRT-ACCS, FAARC, and David L. Vines, MHS, RRT, FAARC

Chapter 12: Noninvasive Ventilation in Pediatrics
Christopher L. Carroll, MD, MS, David A. Turner, MD, and Craig M. Schramm, MD

Chapter 13: Airway Problems of Intubation and Extubation
Shihab Sugeir, MD, Sameer Kamath, MD, and Phillip Lumb, MB, BS, MD, MCCM
CLINICAL DESIGN FEATURES OF MODERN MECHANICAL VENTILATORS

Neil MacIntyre, MD

Objectives

- Understand the three phases of breath delivery: trigger, target, and cycle
- Understand how the various breath designs constitute the common modes of mechanical ventilation
- Understand newer features of partial closed-loop control

INTRODUCTION

Positive-pressure mechanical ventilators have evolved during the past several decades from simple high-pressure gas regulators to sophisticated microprocessor systems controlling many aspects of breath delivery, inspiratory/expiratory timing, and expiratory pressure. Terminology describing these operations has also evolved and is often confusing. Some of this confusion is a consequence of manufacturers' trade names describing a common design feature in multiple proprietary terms. Another problem has been that simple older terminology is unable to fully describe many of the advances that have occurred. Two examples are the mandatory versus spontaneous breath classifications and the concepts underlying controlled versus assisted ventilation. The terms mandatory versus spontaneous originally meant machine alone versus patient alone. Today things are blurred as patients can trigger breaths (spontaneous feature) with substantial ventilator support supplied (mandatory feature). The term control originally meant parameters that the ventilator manipulated (volume- or pressure-controlled). Now the term is often used to distinguish a patient-triggered breath from a machine-triggered breath (assist-control). In this chapter I will generally avoid the terms mandatory and spontaneous and instead use the terms assist and control to mean patient- and machine-triggered breaths, respectively.

BASIC CONCEPTS

Breath Delivery Algorithms

While the engineering principles underlying positive-pressure breath delivery can be quite complex, from a clinical perspective, a mechanical breath can be described in terms of what initiates the breath (trigger variable), what controls gas delivery during the breath (target or limit variable), and what terminates inspiration (cycle variable).

In general, breaths can be initiated (triggered) by patient effort (assisted breaths) or by the machine’s timer (controlled breaths). Effort sensors generally are either pressure or flow sensors and are characterized by their sensitivity/responsiveness. Target or limit variables generally are either a set flow or a set inspiratory pressure. With flow targeting, the ventilator adjusts pressure to maintain a clinician-determined
flow magnitude and pattern (sine, square, accelerating, decelerating); with pressure targeting, the ventilator adjusts flow to achieve and maintain a clinician-determined inspiratory pressure. Modern systems also usually allow adjustment of the rate of pressure rise to the pressure target. Cycle variables are generally a set volume, a set inspiratory time, or a set reduction in inspiratory flow rate as the lung fills during pressure-targeted ventilation. This flow-cycling criterion is either manufacturer specific (eg, 25–35% of peak flow), or clinician-adjusted on many newer machines. A secondary cycling mechanism may be present on some devices if inspiratory time exceeds a certain percentage (eg, 80%) of a set total cycle time without reaching the flow-cycling criterion. Breaths can also be cycled off if pressure limits are exceeded.

With this approach to classifying the inspiratory cycle characteristics, basic breath delivery algorithms from modern mechanical ventilators can be broken into five basic categories of breath: volume control (VC), volume assist (VA), pressure control (PC), pressure assist (PA), and pressure support (PS) (Figure 1).

*Figure 1.* The five basic breaths defined by trigger, target, and cycle variables

![Diagram of basic breaths](image)

Depicted are airway pressure, flow, and volume tracings over time. Solid lines reflect set changes; dotted lines reflect variable changes from effort or mechanics changes. The five basic breaths: 1) volume control is machine triggered, flow targeted, volume cycled; 2) volume assist is patient triggered, flow targeted, volume cycled; 3) pressure control is machine triggered, pressure targeted, time cycled; 4) pressure assist is patient triggered, pressure targeted, time cycled; 5) pressure support is patient triggered, pressure targeted, flow cycled.


**Basic Modes of Ventilatory Support**

The availability and delivery logic of different breath types define the mode of mechanical ventilatory support. The mode controller is an electronic, pneumatic, or microprocessor-based system designed to provide the proper combination of breaths according to set algorithms and feedback data (conditional variables). The five most common modes are volume assist-control ventilation (VACV), pressure assist-control ventilation (PACV), volume-synchronized intermittent mandatory ventilation (V-SIMV), pressure-synchronized intermittent mandatory ventilation (P-SIMV), and stand-alone pressure support ventilation (PSV) (Figure 2). Examples of proprietary
names for these basic modes are given in Table 1.

*Figure 2.* The five basic modes defined by the breaths available

<table>
<thead>
<tr>
<th>BREATH TYPES AVAILABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode</td>
</tr>
<tr>
<td>Volume assist—control</td>
</tr>
<tr>
<td>Pressure assist—control</td>
</tr>
<tr>
<td>Volume SIMV</td>
</tr>
<tr>
<td>Pressure SIMV</td>
</tr>
<tr>
<td>Pressure support</td>
</tr>
</tbody>
</table>

The breaths are the five breaths depicted in Figure 1 plus an unassisted spontaneous breath (Sp). Note that the clinician-set breath rate can result in VACV and PACV being totally controlled ventilation (high set rate), virtually totally assisted ventilation (very low or absent set rate), or assist-control ventilation (intermediate set rate).

Abbreviations: PA, pressure assist; PACV, pressure assist-control ventilation; PC, pressure control; PS, pressure support; SIMV, synchronized intermittent mandatory ventilation; Sp, spontaneous breath; VA, volume assist; VACV, volume assist-control ventilation; VC, volume control.


**TABLE 1.** Examples of Proprietary Names for the Five Basic Modes and Two Feedback Features

<table>
<thead>
<tr>
<th></th>
<th>PB840</th>
<th>Avela/Vela</th>
<th>Servo I</th>
<th>G5</th>
<th>Evita V500</th>
</tr>
</thead>
<tbody>
<tr>
<td>VACV</td>
<td>A/C (VC)</td>
<td>VAC</td>
<td>VC</td>
<td>(S)CMV</td>
<td>VC-AC</td>
</tr>
<tr>
<td>PACV</td>
<td>A/C (PC)</td>
<td>PAC</td>
<td>PC</td>
<td>P-CMV</td>
<td>PC-AC</td>
</tr>
<tr>
<td>VSIMV</td>
<td>SIMV (VC)</td>
<td>VSIMV</td>
<td>SIMV (VC)</td>
<td>SIMV</td>
<td>VC-SIMV</td>
</tr>
<tr>
<td>PSIMV</td>
<td>SIMV (PC)</td>
<td>PSIMV</td>
<td>SIMV (PC)</td>
<td>P-SIMV</td>
<td>PC-SIMV</td>
</tr>
<tr>
<td>PSV</td>
<td>SPONT (PS)</td>
<td>CPAP/PSV</td>
<td>PS/CPAP</td>
<td>SPONT</td>
<td>PC-PSV</td>
</tr>
<tr>
<td>PRVC</td>
<td>VC+</td>
<td>PRVC</td>
<td>PRVC</td>
<td>APV</td>
<td>VC-AC (Autoflow)</td>
</tr>
<tr>
<td>APRVC</td>
<td>BiLevel</td>
<td>BiPhasic</td>
<td>Bi-Vent</td>
<td>APRV</td>
<td>PC-APRV</td>
</tr>
</tbody>
</table>

*Manufacturers: PB840, Medtronics; Avea/Vela, CareFusion; Servo I, Maquet; G5, Hamilton; Evita V500, Draeger Evita.*

Depending upon the set (backup) control breath rate, VACV and PACV can range from totally machine controlled to totally patient assisted. V-SIMV and P-SIMV can provide VA and VC or PA and PC breaths interspersed among either unsupported or PS breaths. Data from international surveys indicate that the most commonly used mode worldwide is VACV, with PACV a distant second. Intermittent mandatory ventilation modes have been steadily decreasing in use while stand-alone PSV modes have been increasing in use.

Choice of mode depends on the clinical goals coupled with an understanding of
ventilator breath design features. Mandatory (backup) breath rates are set based on the patient’s basic ventilation need per minute and the reliability of the patient’s effort to achieve it. The choice of pressure versus flow/volume targeting involves balancing the synchrony enhancement of pressure targeting against the volume guarantee of flow/volume targeting.\(^5\) When using patient-triggered, pressure-targeted breaths, cycling on time (PA breaths) versus flow (PS breaths) depends on patient comfort/synchrony.

Airway pressure release ventilation (APRV) is often touted as a new mode but can be viewed as a variant of P-SIMV in which the inspiratory time is set longer than the expiratory time and the patient is allowed to effectively draw breaths during the high-pressure phase. Patient efforts thus usually occur during the inflation phase and can produce additional unassisted or PS breaths. A point of confusion exists in setting up APRV—dedicated APRV modes on most devices have the set inspiratory pressure referenced to atmospheric pressure rather than the set expiratory pressure as is customary with more conventional modes. Proponents of APRV argue that the long inspiratory-expiratory (I:E) ratio raises mean airway pressure without additional set positive end-expiratory pressure (PEEP) or tidal volume (VT) and that the spontaneous efforts during the inflation phase enhance gas mixing and cardiac filling.\(^8\) Examples of proprietary names are given in Table 1.

### Positive End-Expiratory Pressure

PEEP can be generated in two basic ways: applied or intrinsic. Applied PEEP is set by the clinician and is usually provided by valving systems in the expiratory limb. Modern ventilators also can adjust circuit flow during exhalation to assure PEEP maintenance in the setting of circuit leaks. Intrinsic PEEP develops in the setting of high minute ventilation, short expiratory times, and high airway resistance/high compliance lung units. Total PEEP is the sum of intrinsic PEEP and any PEEP externally set by the clinician. Confusion sometimes develops when intrinsic PEEP is taken to mean total PEEP. Because of this, some use the term *auto-PEEP* instead of *intrinsic PEEP* in settings in which applied PEEP is present. Importantly, applied PEEP distributes evenly throughout the lung, while intrinsic PEEP is highest in high resistance/high compliance lung units and lowest in low compliance/low resistance units.\(^7\) Conventional approaches to PEEP generally rely on set PEEP and avoidance of intrinsic PEEP. However, proponents of APRV argue for the use of intrinsic PEEP to maximize expiratory flow and minimize expiratory time.

### FEEDBACK CONTROL FEATURES

As mechanical ventilators have evolved, the capability has grown for microprocessor-based systems to monitor conditional variables and use this information to automatically adjust timing, flow, pressure, and even fraction of inspired oxygen (Fi\(_{O_2}\)) (feedback control). An early example was the use of a patient effort sensor (conditional variable) to adjust the number of mechanical breaths provided during either assist control modes or SIMV. A variation on this breath rate feedback mechanism was mandatory (or minimum) minute ventilation, which used minute ventilation to adjust the number of positive-pressure breaths delivered. Currently available systems that partially close the loop are described below.
Inspiratory Pressure and Flow Adjustments Based on Artificial Airway Geometry

The endotracheal tube (ETT) imposes a significant inspiratory (as well as expiratory) resistance on a spontaneously breathing patient. This imposed inspiratory load can have an impact on flow synchrony during interactive assisted/supported breaths and can make it difficult to assess potential for ventilator withdrawal during periods of unassisted/unsupported breathing.

Low level (eg, 5–8 cm H$_2$O) PS has been proposed as a way of eliminating the ETT resistive load. However, the PS algorithm supplies a constant inspiratory pressure, which, because of the high fixed resistance of the ETT, tends to undercompensate the load at the beginning of the breath. Moreover, the need varies with minute ventilation. Patient muscle unloading thus is uneven and may be suboptimal.

To better address this loading pattern, many ventilators have the capability to calculate the ETT resistance properties based on clinician input of ETT length and diameter. The ventilator incorporates this calculation with measurements of instantaneous flow to apply pressure proportional to resistance throughout the total respiratory cycle. It must be recognized that the ETT compensation strategy is based on the input geometry of the artificial airway and cannot account for changes in tube characteristics induced by kinks or partial occlusions or the relationship of the tube opening against the tracheal wall.

Feedback Control of Combination Pressure- and Flow-Targeted Breaths

During the past two decades, a number of engineering innovations have attempted to combine the flow synchrony advantages of pressure-targeted breaths with the volume guarantee features of flow-/volume-targeted breaths. The most common approach uses standard pressure-targeted breaths with the ventilator adjusting the pressure target according to a clinician-set Vt. When these breaths are exclusively supplied with time cycling, the mode is commonly referred to as pressure-regulated volume control (PRVC) but has a number of proprietary names (Table 1). When these pressure-targeted breaths are supplied exclusively with flow cycling, the mode is commonly referred to as volume support (VS). Some ventilators switch between these two breath types, depending on the number of patient efforts. The maximum pressure change from breath to breath on most systems generally is limited to a few centimeters of water to prevent sudden large swings in pressure and volume.

These modes have been assessed clinically in two settings. First, in severe parenchymal lung injury (eg, acute respiratory distress syndrome [ARDS]), PRVC has been used as a way to provide more synchronous pressure-targeted breaths while assuring that safe Vt delivery is maintained. One study demonstrated that this was generally possible, although a minority of patients had significant periods of time with Vt that exceeded the targeted value. Second, VS has been touted as a means to automatically wean patients, the theory being that, as patients recover, they will make stronger inspiratory efforts and VS will automatically reduce inspiratory pressure. Conversely, inspiratory pressure would increase if patient effort diminished or respiratory system mechanics worsened. It should be noted that the majority of patients do not benefit from graded withdrawal of machine support. Therefore, whether this approach is superior to routine spontaneous breathing trials is unclear.
Clinicians must also be cautious in using VS in this weaning setting because if the clinician-set volume is excessive for patient demand, a patient may not attempt to take over the work of breathing for that volume and thus support reduction, and weaning may not progress. In addition, if the pressure level increases in an attempt to maintain an inappropriately high set VT in the patient with airflow obstruction, an increase of intrinsic PEEP may result. VS may also inappropriately lower inspiratory pressure in a patient with excessive flow demands induced by pain, anxiety, or acidosis.11

Enhanced Feedback Control of Combination Pressure- and Flow-Targeted Breaths

Monitoring of airway occlusion pressure, oxygen saturation, and end-tidal CO$_2$ concentrations have been incorporated in various fashions into the pressure-flow/volume hybrid breaths described above.12 One commercial system uses end-tidal CO$_2$ and respiratory rate along with the VT to adjust the applied inspiratory pressure (SmartCare). This system attempts to find an inspiratory pressure that maintains the respiratory rate and VT in a clinician-set “comfort zone,” adjusting it as necessary. The end-tidal CO$_2$ serves as a backup signal to ensure adequate ventilation. Inspiratory pressure is reduced to as low a level as possible within these boundaries. The system will alert the clinician to perform a spontaneous breathing trial when this pressure reaches 9 cm H$_2$O. Although clinical trials have failed to consistently show an advantage to this approach,13 an automated system that is just as good as clinicians could have applications in settings of rapidly recovering patients or low availability of clinicians to make frequent assessments.

Feedback Control of Ventilator Breath Delivery Based on Respiratory System Mechanics

A novel approach to automated feedback control of ventilator support controls a pressure-targeted breath using a VT, frequency, and I:E ratio algorithm based on respiratory system mechanics. The objective is to help the patient maintain an efficient and effective breathing pattern. Known as adaptive lung ventilation or adaptive support ventilation (ASV),12 the system calculates respiratory system mechanics using several controlled test breaths. It then uses a “minimal work” calculation14 to set the frequency-VT pattern that minimizes the combined resistance and compliance components of work. The ASV algorithm then attempts to minimize intrinsic PEEP by measuring the expiratory time constants (RCe) (RCe = resistance x compliance) and providing an expiratory time of at least three RCes.

With ASV, clinicians must set the desired minute ventilation and the proportion of that minute ventilation that the machine is to supply. Ideal body weight also can be used to calculate the desired minute ventilation based on metabolic demands and predicted dead space. Clinicians practicing in the United States also must set the PEEP and FiO$_2$. When spontaneous efforts occur with ASV, the algorithm responds with fewer mandatory breaths and adjusts inspiratory pressure according to the minimal work VT considerations above. ASV has been shown to perform as designed. In healthier lungs, VTs may exceed lung-protective guidelines.12 There are no meaningful outcome studies showing clear benefit.
**Feedback Systems Controlling PEEP and FIO₂**

On a mechanical ventilator, an FIO₂ controller conceptually could be coupled to a feedback controller of PEEP to meet oxygenation and mechanical goals (ie, partial arterial oxygen pressure [Pao₂] or oxygen saturation targets balanced against lung compliance or plateau pressure). One system approved outside the United States incorporates the PEEP-FIO₂ table used by the National Institutes of Health ARDS Network study. With this algorithm, PEEP and FIO₂ combinations are guided by a partial arterial oxygen pressure target range of 55–80 mm Hg and a plateau pressure limit of 30–35 cm H₂O. While this table proved safe and effective in ARDS Network trials, it has yet to be demonstrated whether an automated system using it will improve outcomes.

**MODES DRIVEN BY NOVEL SENSORS OF PATIENT EFFORT**

Two new modes have recently been introduced that use unique feedback control based on patient effort to control positive-pressure breath delivery. The first is proportional assist ventilation (PAV), an approach that applies a clinician-set pressure and flow “gain” on patient-generated flow and volume. PAV uses intermittent controlled “test breaths” to calculate resistance and compliance. It can then use measured flow and volume to calculate both resistive and elastic work. The clinician is required to set a desired proportion of the total work that should be performed by the ventilator. The ventilator continuously measures the patient flow and volume during each breath, adding sufficient flow and airway pressure to achieve the selected proportion of the breathing work. The combined application of pressure and flow distinguishes it from PSV, which applies variable flow and a clinician-set fixed airway pressure. PAV has been compared to power steering on an automobile, an apt analogy. Like PAV, power steering reduces the work to turn the wheels but does not automatically steer the car; the driver must control the car’s ultimate direction just as the patient ultimately must control the magnitude of the breath and the timing of the breathing pattern. Newer PAV modifications (PAV+) automatically revise machine output by recalculating tidal mechanics periodically during a brief occlusion applied at the start of exhalation. In this way, the clinician simply has to select the percentage of the breathing workload that the machine should supply.

Because PAV requires sensors in the ventilator circuitry to measure patient effort, it is susceptible to the same sensor performance and intrinsic PEEP issues that affect breath triggering in other assisted modes. Also like conventional assisted modes, the clinician must set PEEP and FIO₂. Finally, breath termination (cycling) is much like pressure support and is determined by a clinician-adjustable percentage of maximal inspiratory flow.

In multiple studies, PAV has been shown to perform as designed. However, whether PAV improves meaningful clinical outcomes (eg, sedation needs, shorter duration of mechanical ventilation) remains to be determined.

A second novel mode is neurally adjusted ventilatory assist (NAVA), which uses a diaphragmatic electromyography (EMG) signal to trigger, govern flow, and cycle ventilatory assistance. The EMG sensor is an array of electrodes mounted on a catheter that is positioned in the esophagus at the level of the diaphragm. Ventilator
breath triggering is thus virtually simultaneous with the onset of phrenic nerve excitation of the inspiratory muscles, and breath cycling is tightly linked to the cessation of inspiratory muscle contraction. Flow delivery is driven by the intensity of the EMG signal (electrical activity of the diaphragm) and the clinician sets an mL/mV gain factor. Output from the catheter provides a unique means of tracking inspiratory and expiratory neural timing and has been used effectively in recent research for this purpose.

Like PAV, NAVA depends exclusively on patient effort for timing, intensity, and duration of the breath. Thus, like PAV, clinicians must set appropriate alarms and backup positive-pressure ventilation, especially for patients with unreliable respiratory drives. Also like PAV, clinicians must set PEEP and $F_{O_2}$.

NAVA has been shown to perform as designed and, conceptually, it should provide excellent patient-ventilator synchrony. However, data are lacking that demonstrate improved outcomes (e.g., duration of mechanical ventilation, sedation needs). Another concern with NAVA is the expense associated with the EMG sensor.

**DESIGN CONSIDERATIONS FOR PEDIATRIC/NEONATAL APPLICATIONS**

Design features for pediatric and neonatal applications are similar to those already described for adult applications. However, mechanical ventilation of pediatric patients (especially neonates) does require a number of adjustments to device performance specifications and sometimes availability of specific modes.

Specific differences among adult, pediatric, and neonatal operations usually involve the available ranges for breath rates, Vts, flows, breath timing, and alarm configurations. In general, pediatric (especially neonatal) applications require faster breath rates, smaller Vts, lower maximal flows, and shorter inspiratory times. These capabilities require flow sensor technology that is able to accurately measure flow to less than 30 mL/min and volumes to less than 2 mL. Displays must be modified accordingly. To ensure accurate monitoring, it is also advisable to use proximal flow sensors, especially in neonates, whose respiratory system compliances are often lower than the breathing circuit.

Pediatric and neonatal mechanical ventilator strategies generally do not include modes such as PRVC or APRV. Instead, a popular mode, especially for neonates, is time-cycled, pressure-limited ventilation—a pressure-targeted mode that requires clinician input for inspiratory flow and duration.

In the past, these features often required a dedicated pediatric or neonatal ventilator. Modern devices, however, are usually capable of providing the necessary range of performance capabilities and can be configured by the operator to support patients across the age spectrum.

**KEY POINTS**

- The goal of mechanical ventilation is to provide positive-pressure breaths to the lungs that are adequate for gas exchange and appropriate muscle unloading while minimizing any risk for injury or discomfort.
- In general, breaths can be initiated (triggered) by patient effort (assisted breaths)
or by the machine’s timer (controlled breaths).

- The latest generation of ventilators uses sophisticated feedback systems to "sculpt" positive-pressure breaths according to patient effort and respiratory system mechanics to accomplish these goals.
- At present, new control strategies are not totally closed-loop systems because the automatic input variables are still limited, some clinician settings are still required, and the specific features of the perfect breath design still are not entirely clear.
- Despite these limitations, there is at least some rationale for many of the newer feedback features, even though virtually all of them await outcome studies to further justify their widespread use.

REFERENCES

16. Sinderby C, Beck J. Proportional assist ventilation and neurally adjusted ventilatory assist—


Chapter 2

THE CONCEPT OF LUNG PROTECTIVE VENTILATION/MANAGING ACUTE LUNG INJURY AND PARENCHYMAL LUNG DISEASE IN ADULT AND PEDIATRIC PATIENTS

Sean Levy, MD, Ira Cheifetz, MD, Kathryn Hibbert, MD

Objectives

- Understand the physiologic mechanisms of ventilator-induced lung injury (VILI)
- Understand initial ventilator management to prevent VILI in acute respiratory failure/acute lung injury
- Understand ongoing monitoring parameters and subsequent adjustments and adjunctive therapies to treat VILI

INTRODUCTION

Acute respiratory distress syndrome (ARDS) remains quite common and highly morbid, with an annual incidence of more than 170,000 cases in the United States alone and a mortality that is often greater than 30%.1 Although our understanding of ARDS pathophysiology has improved significantly, with pathways of injury, coagulation, and inflammation now elucidated, there remain no specific drug therapies.2 Supportive care with mechanical ventilation, therefore, remains the mainstay of therapy for ARDS. However, it is increasingly recognized that mechanical ventilation is an independent cause of lung injury and can worsen preexisting ARDS.3 Careful attention to management of the mechanical ventilator is therefore essential to reducing ARDS-associated morbidity and mortality.

ADULT CASE VIGNETTE

A 62-year-old woman with a history of morbid obesity and rheumatoid arthritis with associated interstitial lung disease presents with a four-day history of fever, myalgia, productive cough, and shortness of breath. In the emergency department, chest radiograph shows bilateral airspace infiltrates consistent with ARDS. Rapid diagnostic testing is positive for influenza. Broad-spectrum antibiotics and antiviral therapy are initiated. She remains hypoxemic despite the use of high-flow nasal cannula for oxygenation. Endotracheal intubation is performed urgently, and mechanical ventilation is initiated on volume control mode, with tidal volume (Vt) set at 6 mL/kg ideal body weight (IBW), rate 20 breaths/min, fraction of inspired oxygen (FIO2) 1.0, and positive end-expiratory pressure (PEEP) 8 cm H2O. Her measured end-inspiratory plateau pressure (Pplat) is 36 cm H2O. She remains hypoxemic despite the use of high-flow nasal cannula for oxygenation. Endotracheal intubation is performed urgently, and mechanical ventilation is initiated on volume control mode, with tidal volume (Vt) set at 6 mL/kg ideal body weight (IBW), rate 20 breaths/min, fraction of inspired oxygen (FIO2) 1.0, and positive end-expiratory pressure (PEEP) 8 cm H2O. Her measured end-inspiratory plateau pressure (Pplat) is 36 cm H2O. She remains hypoxemic, with arterial partial pressure of oxygen (Pao2) 48 mm Hg on FIO2 1.0. Esophageal manometry is performed, revealing an end-expiratory transpulmonary pressure of −4 cm H2O and end-inspiratory transpulmonary pressure of +13 cm H2O. On a PEEP of 15 cm H2O, her respiratory system compliance (Crs) was also noted to be optimized.
(stress index 1.03) compared to both higher and lower PEEP (stress index 1.19 and 0.78, respectively). Based on these measurements, the PEEP is increased to 15 cm H₂O. The patient is also administered neuromuscular blocking agents and placed in the prone position. With these interventions, subsequent improvements in oxygenation are noted. She is successfully extubated on day nine of intubation.

**PEDIATRIC CASE VIGNETTE**

A previously healthy eight-year-old girl presents to the emergency department with a two-day history of fever, cough, poor oral intake, and general malaise. Chest radiograph shows significant bilateral airspace disease without focal infiltrate. Rapid diagnostic testing is positive for influenza. Blood cultures are obtained, along with a respiratory polymerase chain reaction viral assay. Broad-spectrum antibiotics and antiviral therapy are initiated. She is admitted to the pediatric intensive care unit (ICU) on noninvasive ventilatory support. Over the next few hours, her work of breathing worsens, and the FIO₂ requirement increases. She is intubated and placed on synchronized intermittent mandatory ventilation in pressure control mode. The peak inspiratory pressure is set at 18 cm H₂O above PEEP (10 cm H₂O). The mean airway pressure is 14 cm H₂O. Vt, as measured by a pneumotachometer placed between the ventilator circuit and the endotracheal tube, is 6 mL/kg IBW. Ventilator rate is set at 24 breaths/min, and the FIO₂ is 1.0. The patient’s arterial blood gas analysis shows: pH 7.28, arterial partial pressure of carbon dioxide (Paco₂) 58 mm Hg, Pao₂ 60 mm Hg. The resultant oxygenation index is 23. The respiratory polymerase chain reaction viral study is positive for type A influenza. The patient is sedated with fentanyl and dexmedetomidine infusions but does not receive additional neuromuscular blockade (NMB) after an intubation dose.

Over the next 12 hours, she remains hypoxemic, with the FIO₂ weaned to only 0.80. The oxygenation index remains in the low 20s. A PEEP titration is performed while monitoring oxygenation, hemodynamics, and mixed venous lactate measurements. It is determined that optimal PEEP is 14 cm H₂O. Dynamic compliance improves with the peak inspiratory pressure remaining at 28 cm H₂O, despite the increased PEEP. Over the next four days, the patient’s respiratory process resolves, and she is uneventfully extubated on hospital day eight. She is discharged home four days later on no respiratory support.

**DEFINITION OF ACUTE RESPIRATORY DISTRESS SYNDROME AND TYPES OF VENTILATOR-INDUCED LUNG INJURY**

ARDS is a clinical syndrome defined by the acute onset of bilateral pulmonary infiltrates and hypoxemia not solely attributable to cardiogenic pulmonary edema. The classic pathophysiology is defined by alveolar-capillary membrane breakdown with the subsequent influx of protein-rich plasma, formation of hyaline membranes, and loss of alveolar stability. ARDS can result from a variety of stimuli, including trauma, pulmonary or extrapulmonary infection, and other inflammatory conditions such as pancreatitis and blood product transfusion. Most patients require mechanical ventilatory support, either invasively or noninvasively, for hypoxemic respiratory failure.

Although mechanical ventilation can be lifesaving, the very act of ventilating
someone via positive pressure can cause and propagate lung injury in a process broadly termed ventilator-induced lung injury (VILI) or ventilator-associated lung injury (VALI). The relative importance of VILI is increasingly recognized, particularly since studies have shown a mortality benefit to specific lung-protective ventilator strategies. Additionally, it is now recognized that VILI can result in ARDS in susceptible patients. As a result, and in the absence of specific drug therapies to prevent and treat ARDS, significant emphasis should be placed on ventilator strategies that protect the lung and minimize secondary damage and inflammation. The two primary theoretical mechanisms of VILI are excess stress, defined in physical terms as the force per unit area, and excess strain, defined as mechanical deformation (in the lung, volume change).

The primary mechanism of lung injury is thought to be overdistention and excess local strain; there is limited evidence that high pressure alone is injurious. However, because high airway pressures often reflect local overdistention, some lung injury is categorized as barotrauma, indicating injury from high pressures. Pneumothorax, pneumomediastinum, and subcutaneous emphysema are all examples of classical barotrauma. Although these are unlikely to occur without regional volume change, there are some sequelae of ventilation at high pressures that are true manifestations of high intrathoracic pressure. These include a potential decrease in cardiac output due to decreasing venous return and an increase in physiologic dead space as alveolar pressure exceeds pleural pressure.

The other large category of VILI is volutrauma, referring to excess volume change, either globally or regionally, that results in injury and increased circulating inflammatory mediators. Volutrauma can result either from the use of large tidal volumes or the delivery of smaller volumes into a heterogeneous lung, resulting in regional overdistention. The risk of volutrauma is particularly high in ARDS, in which there can be a significant reduction in the volume of aerated lung, or functional lung size, sometimes referred to as the “baby lung.” There is strong evidence that limiting tidal volumes and scaling them to IBW improves outcomes in ARDS patients, but it remains difficult to measure regional overdistention. Therefore, a number of proxy measurements have been implemented to limit injurious overdistention including driving pressure (ΔP), or Vt/Crs), which scales tidal volume to lung volume.

Two other categories of common VILI include atelectrauma and biotrauma. Atelectrauma results from the cyclic opening and closing of lung units, resulting in shear stress and strain in the form of cellular deformation. Although there is some debate about the degree of lung collapse versus the filling of lung units with fluid and cells, the movement of a column of fluid in and out of alveoli could result in similar shear stress. Based on this theoretical mechanism of injury, and on the experimental observation that ventilation at a low PEEP promotes lung injury, significant attention is focused on preventing de-recruitment, or loss of aerated lung volume, with the use of PEEP. Biotrauma refers to the inflammatory cascade that results from mechanical ventilation and that can propagate lung injury as well as other organ failure. It is notable that most patients who die of ARDS do not die from hypoxemia but rather from other organ failure, suggesting that normalizing blood gases may be an insufficient guideline for ventilator strategies.

Other commonly set ventilator parameters include FIO2 and respiratory rate. Inhalation of hyperoxic gas over a prolonged period has been well demonstrated in
animals to cause hyperoxic acute lung injury, and it is suspected that prolonged exposure to a high F\textsubscript{O}_2 is injurious in humans as well.\textsuperscript{10} Hyperoxia is thought to cause lung injury via increased production of reactive oxygen species and increased oxidative stress. Hyperoxia has previously been demonstrated to cause alveolar epithelial cell death and capillary endothelial dysfunction. There also appears to be a synergistic effect between hyperoxia and strain in promoting lung injury.\textsuperscript{10} However, despite convincing animal data for the role of hyperoxia in lung injury, there have been no randomized studies of F\textsubscript{O}_2 levels or levels of oxygen saturation in humans with ARDS. In prior studies, it has been difficult to distinguish whether patients worsened because of high F\textsubscript{O}_2 or received high F\textsubscript{O}_2 because of the severity of their illness. It is nevertheless reasonable to attempt to use the minimum necessary F\textsubscript{O}_2 to maintain safe oxygenation (Pao\textsubscript{2} > 55 mm Hg).

When setting the respiratory rate on the ventilator, the primary concern should be maintenance of adequate minute ventilation, which may be a challenge with low Vts. There are not thought to be any adverse sequelae to the frequency of breathing normally used in mechanically ventilated patients (respiratory rate 10–35 breaths/min), although in patients with obstructive disease, a higher respiratory rate may result in more dynamic hyperinflation and the development of intrinsic PEEP. However, most patients with ARDS without underlying obstructive disease have normal airway resistance, and intrinsic PEEP is absent or minimal across a range of breathing frequencies.

The overall lung-protective strategy, therefore, focuses on minimizing regional and global overdistention and reducing cyclic opening and collapse while using the minimal necessary F\textsubscript{O}_2. This lung-protective strategy, often summarized as an “open lung” approach, often comes at the cost of deep sedation, which is increasingly recognized to be associated with poor outcomes, including prolonged weakness (i.e. critical illness myopathy), impaired functional status, and adverse cognitive and psychological outcomes.\textsuperscript{11,12} However, there remains strong evidence for improved outcomes with lung-protective ventilator settings. For example, there is epidemiologic evidence for a decreased incidence of iatrogenic ARDS since the standardization of low Vt ventilation and a growing surgical literature suggesting a mortality benefit to low Vt ventilation even in those without preexisting lung injury. Strategies for reducing VILI, therefore, remain a cornerstone of therapy for patients with ARDS and other types of respiratory failure.

**INITIAL STRATEGIES TO REDUCE VENTILATOR-INDUCED LUNG INJURY**

*Low Tidal Volume Ventilation*

A landmark study from the ARDS Network (ARDSNet)\textsuperscript{6} in 2000 that was designed based on data from similar prior smaller studies, examined the use of low Vt (lung-protective) ventilation in patients with ARDS (Pao\textsubscript{2}/FiO\textsubscript{2} ratio [P/F] < 300 mm Hg). Conventional ventilation approaches traditionally used larger Vts of 10–15 mL/kg of body weight to ensure normalization of the Paco\textsubscript{2} and serum pH. The ARDSNet investigators theorized that these larger Vts, greater than those of healthy people (5–8 mL/kg of body weight), might contribute to excessive distention of the aerated portions of the lung (i.e. volutrauma), leading to lung injury through a variety of mechanisms, as had previously been demonstrated in animal studies. Given the
large non-aerated dependent portions of the injured ARDS lung, Vt targets might need to be even lower than in normal subjects.

In this double-blind, randomized, controlled trial of 861 patients, subjects in the experimental arm were assigned to an initial targeted Vt of 6 mL/kg (with a range of 4–8 mL/kg) IBW (based on height and gender) and a target Pplat of 30 cm H$_2$O or less, while those in the control arm received an initial Vt of 12 mL/kg (with a range of 4–12 mL/kg) IBW and a target Pplat of 50 cm H$_2$O or less. Compared with the control group, those in the lung-protective ventilation group had an absolute reduction of 9 percentage points in the rate of death before a patient was discharged home and was breathing without assistance (39.8% vs. 31.0%, $p = 0.007$). Ventilator-free days were also greater in the lung-protective group. Mean Vts were 11.8 mL/kg in the control group and 6.2 mL/kg in the lung-protective group, although there was a less substantial difference in mean Pplats (33 vs. 25 cm H$_2$O, respectively).

Serum interleukin-6 concentrations (known to play a role in lung inflammation and injury via biotrauma) were lower in the lung-protective arm, despite higher PEEP and $\text{FiO}_2$ requirements and lower P/F. The authors theorized that mortality benefit may have been mediated by a reduction in systemic inflammation and therefore fewer organ failures. The improved outcomes in this study are greater than the benefit seen with any single intervention in any other ARDS study. Lung-protective ventilation has since become the standard of care for patients with ARDS.

Improved outcomes have also been observed in surgical populations receiving lung-protective ventilation. Studies are ongoing to determine the effectiveness of low Vt ventilation in the prevention of ARDS in subjects without evidence of lung injury but with risk factors for its development. While most trials have been performed using volume control ventilation, other modes of ventilation, such as pressure control, may be used with lung-protective ventilation, but close attention should be paid to the delivered Vt to ensure that it remains within the safe range of 4–8 mL/kg IBW.

In the pediatric population, low Vt ventilation has not been studied in a randomized, controlled fashion. The Pediatric Acute Lung Injury and Consensus Conference (PALICC) recommended the use of Vts in or below the range of physiologic Vts for age/IBW (ie, 5–8 mL/kg). PALICC further recommended that this range be adjusted based on the patient's lung pathology and Crs with Vts of 3–6 mL/kg IBW for those pediatric patients with more severe ARDS. Until more definitive data are available for pediatric ARDS, it seems reasonable to follow the adult-based, low Vt data and the recommendations from PALICC.

**High Versus Low Positive End-Expiratory Pressure**

VILI may occur through a variety of mechanisms, including atelectrauma, or large shear forces produced by repetitive recruitment (opening) and derecruitment (collapse) of alveoli. The functions of PEEP in mechanical ventilation include alveolar recruitment and the prevention of derecruitment, decreased cyclic airway opening and end-expiratory collapse improving ventilation homogeneity, redistribution of extravascular lung water, and protecting lung surfactant, thereby reducing alveolar surface tension. Higher levels of PEEP (greater than 12 cm H$_2$O) were traditionally avoided because of the risk of hemodynamic instability related to reduced venous return from higher intrathoracic pressure, along with the risk of barotrauma and
pneumothorax with high airway pressures. However, the lung-protective ventilation group in the 2000 ARDSNet study received higher levels of PEEP and demonstrated no evidence of deleterious effects as a result.

Based on these data, another ARDSNet double-blind, randomized, controlled trial was designed, targeting a low versus high PEEP strategy in patients with early ARDS (P/F < 300 mm Hg). Both arms received lung-protective ventilation (Vt goal 6 mL/kg IBW, target Pplat < 30 cm H₂O), but oxygenation targets were obtained using different PEEP and FiO₂ tables. Mean (±SD) PEEP values were 8.3 ± 3.2 cm H₂O in the low PEEP arm and 13.2 ± 3.5 cm H₂O in the high PEEP arm, with no difference in adverse events noted between the groups. There was no difference in the primary outcome of death before discharge home while breathing without assistance (24.9% in the low PEEP arm, 27.5% in the high PEEP arm, p = 0.48). In addition, no difference was seen in the number of ventilator-free days between the groups.

Because this study included all patients with ARDS (mild, moderate, and severe), and given the theory that higher PEEP levels would be of greater benefit in those with more severe ARDS, a more recent meta-analysis of three randomized controlled trials of high versus low PEEP strategy, consisting of almost 2,300 patients with ARDS, was performed. In addition to the 2004 ARDSNet study, this analysis included two additional trials, the Lung Open Ventilation trial and the Express study. In the Lung Open Ventilation trial, subjects in the experimental group were allowed a higher maximum Pplat of 40 cm H₂O and included recruitment maneuvers and higher PEEP targets than the control group. All subjects received low Vt ventilation. In the Express study, subjects also received low Vts but were randomized to low PEEP (5–9 cm H₂O) versus titrating PEEP to achieve a Pplat of 28–30 cm H₂O. While no overall difference was seen in hospital deaths between the low and high PEEP strategies in the meta-analysis, a beneficial effect for high PEEP was demonstrated in those with P/F < 200 mm Hg (previously defined as ARDS, with P/F 200–300 mm Hg defined as acute lung injury), with a rate of hospital death of 34.1% in the high PEEP group and 39.1% in the low PEEP group (p = 0.049). Rates of barotrauma and vasopressor use were similar in the two groups.

Similar to the situation with low Vt ventilation, definite data are lacking for PEEP management in pediatric ARDS patients. PALICC recommended “moderately” elevated levels of PEEP, defined as 10–15 cm H₂O, for patients with severe pediatric ARDS, titrated to the observed oxygenation and hemodynamic response. PALICC further recommended that PEEP levels higher than 15 cm H₂O may be needed for severe pediatric ARDS, with close attention paid to limiting the Pplat and monitoring markers of oxygen delivery, Crs, and hemodynamics.

**Personalized PEEP Titration**

One suspected reason that comparisons of high versus low PEEP strategies have not shown benefit in large studies is that while some patients benefit from higher PEEP, others, with less recruitable lungs, may experience only the adverse effects of overdistention. One strategy to set PEEP in individual patients is, therefore, to identify a PEEP where physiologic parameters are optimized. There are multiple personalized PEEP titration approaches, including esophageal manometry, PEEP
titration to best tidal compliance, calculated stress index, and titration of PEEP and Vt to a minimal driving pressure.

The optimal mode for bedside titration of PEEP has not been clearly established in the adult or pediatric population. In a novel, well-designed study conducted at two centers between 2008 and 2011, 51 adult subjects with ARDS received standardized ventilator management with the exception of randomization of the mode of bedside PEEP titration, along with computed tomography of the chest to determine the degree of lung recruitability. All subjects received NMB throughout the study as well as an initial recruitment maneuver followed by low Vt ventilation. Four different PEEP titration strategies were tested, including the oxygenation-based Lung Open Ventilation strategy PEEP/F\(\text{Io}_2\) tables (using the higher PEEP table previously studied), esophageal manometry, increasing the PEEP until a Pplat of 28–30 cm H\(\text{2}O\) was achieved (maintaining Vts at 6 mL/kg IBW), and adjusting PEEP according to the stress index. Using the Lung Open Ventilation tables, PEEP was lower in those with mild ARDS and higher in those with severe ARDS (8 ± 2 vs. 15 ± 3 respectively, \(p < 0.05\)), with a weak relationship to lung recruitability (\(r^2 = 0.29, p < 0.0001\)). PEEP was similarly high regardless of ARDS severity when the other three strategies were used, with no relationship to lung recruitability. Until better data are available to guide the choice of PEEP titration method, the preferred method for any clinician should be based on available local expertise and technology.

**Esophageal Manometry**

Two primary mechanisms of lung injury are volutrauma and atelectrauma, both of which should be reflected in derangements in transpulmonary pressure (defined as the difference between airway opening pressure and Pplat, the distending pressure of the lung). Critically ill patients, particularly those with volume overload, intra-abdominal hypertension, and obesity, can have unpredictable and often elevated pleural and abdominal pressures. This can lead to a net negative end-expiratory transpulmonary pressure, which signifies a net balance of pressures that promotes collapse and possibly atelectrauma. Conversely, if a patient has high end-inspiratory transpulmonary pressure, this signifies a high distending pressure of the lung and possible overdistention.

Esophageal manometry has been proposed as a surrogate for pleural pressure to aid in this decision-making process. Esophageal balloon measurements are limited in their accuracy by cardiac oscillations, esophageal contraction, and the position of the catheter in a gravitationally dependent position potentially under the weight of the mediastinum. Despite these limitations, previous animal and healthy human data suggest that its measurement might be beneficial in the management of mechanically ventilated critically ill patients. A single-center pilot study randomized adult subjects with ARDS to either conventional PEEP titration using ARDSNet tables versus PEEP titration according to esophageal manometry.

The trial was stopped after 61 subjects were enrolled because the primary end point of oxygenation at 72 hours was significantly better in the esophageal manometry arm (\(P/F 280 \text{ mm Hg for esophageal manometry, 191 mm Hg for conventional titration, } p = 0.002\)). Oxygenation was better in the esophageal manometry arm at all time points (24–72 hours), and PEEP was higher in the esophageal manometry group at 72 hours (18 ± 5 for the esophageal manometry group, 12 ± 5 for the conventional...
titration group, \( p < 0.001 \)). PEEP titration by esophageal balloon resulted in a net positive transpulmonary pressure. There were no signs of overdistention in the esophageal manometry group, despite the overall higher PEEP, and, in fact, Crs was increased in the esophageal manometry group (\( p = 0.01 \)), suggesting a net recruitment of lung. There was also a trend toward improved survival in the esophageal manometry group. Given these promising results, a multicenter randomized clinical trial is currently under way to better elucidate the utility of esophageal manometry in the titration of PEEP in patients with ARDS. Notably, the first study compared esophageal manometry to a low PEEP/F\(_{\text{IO}_2}\) table whereas the ongoing trial uses a higher PEEP/F\(_{\text{IO}_2}\) table for comparison. Unfortunately, similar data are not available in the pediatric population.

**Stress Index**

Stress index is a dimensionless coefficient that describes the slope of the time-pressure curve of the respiratory system.\(^{22}\) In essence, it describes whether, with a constant change in volume, the change in pressure per unit volume is constant, decreasing or increasing during the inhalation—ie, whether Crs remains stable, increases, or decreases. A value less than 1 indicates improving Crs over the breath, suggesting lung recruitment. A value greater than 1 indicates decreasing Crs over the breath, suggesting lung overdistention. A value equal to 1 reflects stable Crs with neither net recruitment nor net overdistention. In an animal model of lung injury in which a recruitment maneuver was followed by PEEP titration to a target stress index, the stress index values correlated significantly with tidal recruitment and tidal hyperinflation as measured by computed tomography evaluation of lung density (\( R = 0.917 \) and \( R = 0.911, p < 0.0001 \)).\(^{22}\) The major limitation to this method of PEEP titration remains the availability of software to analyze the airway pressure-time curve.

**Best Tidal Compliance**

Since the goal is to increase PEEP only as long as it provides the benefit of recruitment and without overdistention, one strategy is to titrate PEEP directly to Crs, calculated as \( \text{Crs} = \frac{\text{Vt}}{(\text{PEEP} – \text{Pplat})} \). Using volume control ventilation mode, PEEP is titrated to optimal Crs, which has also been shown to optimize oxygen delivery and minimize shunt fraction and dead space.\(^8\) This strategy was first described decades ago but remains in clinical practice because of the ease of bedside measurements. However, it does require a fully passive patient to obtain reliable Pplat values.

**Driving Pressure**

Since the two determinants of pulmonary overdistention are PEEP and Vt, one method to minimize pulmonary overdistention is a combined titration of both parameters to Crs. One retrospective study of nine adult ARDS trials examined whether driving pressure (\( \Delta P \)), defined as Vt divided by Crs, was associated with outcome.\(^{23}\) In patients not making spontaneous breathing efforts, \( \Delta P \) is calculated as Pplat minus PEEP. This study demonstrated that, among ventilation variables (PEEP, Pplat, and \( \Delta P \)), \( \Delta P \) was most strongly associated with survival. Elevated \( \Delta P \), even in the context of “protective” Vt and Pplats, was associated with increased mortality. Additionally, changes in PEEP or Vt were correlated with outcomes only if
ΔP changed as well. The authors theorized that ΔP was so strongly predictive of outcomes because it incorporates both the net effect of PEEP (recruitment vs. overdistention) and a measure of whether Vt is appropriately scaled to the proportion of lung available to ventilation or functional lung.

**Recruitment Maneuvers**

Recruitment maneuvers involve temporarily inducing a higher transpulmonary pressure than that seen with tidal breathing. Similar to PEEP titration, the major limitation to recruitment maneuvers is the risk of barotrauma/pneumothorax and hemodynamic instability (ie, hypotension) related to an elevated mean intrathoracic pressure. There is no standardized approach to conducting a recruitment maneuver. Variations in duration, maximum pressure, and end-expiratory pressure have been reported. This variability, combined with the fact that these maneuvers are usually studied as part of a broader ventilator management strategy, has limited the ability of investigators to detect a clear signal as to their utility for adult or pediatric ARDS patients. In general, the maneuver usually consists of providing approximately 20–60 seconds of 30–40 cm H₂O continuous positive airway pressure before returning to prior tidal ventilation. Some of the studies to date have placed limitations on Vt and Pplat, while others have not.

A 2009 Cochrane review assessed a total of seven trials comprising 1,170 subjects. All seven trials included a recruitment maneuver for the management of mechanically ventilated patients with ARDS. Two of the trials included an alternative ventilator management strategy in addition to the recruitment maneuver (as compared with standard of care). There was no significant difference in 28-day mortality in those who received a recruitment maneuver. Importantly, there was also no difference in rates of barotrauma or hypotension in these pooled data. There were insufficient data on outcomes, such as duration of mechanical ventilation and hospital stay, in the pooled data, but individual studies did not demonstrate a benefit with regard to mortality or duration of mechanical ventilation or hospitalization. In those studies that measured changes in oxygenation following these maneuvers, there was a temporary (maximum time measured from maneuver was 24 hours) improvement in arterial oxygenation. The significance of this change is not clear, since the recruitment maneuver not only may have recruited alveoli for ventilation but also may have caused overdistention and subsequent VILI that became evident more than 24 hours after the maneuver.

Additionally, if a recruitment maneuver is performed without subsequent appropriate PEEP titration, then lung recruitment may be temporary. Additional studies are needed before recruitment maneuvers can be recommended as part of a standardized approach to the ventilator management of adult or pediatric patients with ARDS. It remains unclear whether recruitment maneuvers offer benefit over the more standard approaches to PEEP titration. It also remains unknown whether short-term high transpulmonary pressures may contribute to VILI and whether any such injurious effects outweigh improvements in oxygenation.

**High-Frequency Oscillatory Ventilation**

Based on the knowledge that repetitive overdistention and alveolar collapse contribute to VILI, a strategy of high-frequency oscillatory ventilation (HFOV) has
been studied in a number of trials. HFOV uses very small Vts (usually 1–2 mL/kg) delivered at very high rates (5–15 breaths/sec). In the past, it had been used as a rescue strategy for those patients with severe ARDS who did not respond to conventional ventilation strategies. A number of early small trials compared HFOV with conventional ventilation (which did not use low Vt ventilation strategies), finding some degree of benefit.

A multicenter, randomized, controlled trial (OSCILLATE) was conducted in which adult patients with early moderate to severe ARDS (P/F < 200 mm Hg) were assigned to HFOV or lung-protective ventilation, with those in the conventional arm having the ability to cross over to HFOV for salvage therapy. The trial was stopped early on the recommendation of the data-monitoring committee after 548 of the planned 1,200 subjects had been enrolled. The two study groups were well matched, and 12% of those assigned to conventional ventilation crossed over to receive HFOV. In-hospital mortality was 47% in the HFOV group and 35% in the conventional ventilation group, with a relative risk for HFOV of 1.33 (95% CI, 1.09–1.64, \( p = 0.005 \)). Higher rates of sedative, NMB, and vasopressor use were noted in the HFOV group. HFOV frequency was maximized to minimize Vts, and mean airway pressures were higher in the HFOV group, potentially providing some explanation for the increased mortality. Based on this and other similar negative studies, HFOV cannot be recommended for first-line treatment of moderate to severe ARDS in the adult population.

The use of HFOV for pediatric ARDS remains controversial. Some pediatric intensivists critique the OSCILLATE study for the high number of patients with sepsis, the relative inexperience with HFOV of many clinicians in the multiple sites, and the significant need for vasoactive agents in the HFOV group. The inclusion of such patients and the use of a high mean airway strategy may explain the increased risk of mortality with HFOV in this adult population.

PALIICC recommended that HFOV should be considered as an alternative approach for acute hypoxemic respiratory failure in pediatric patients with moderate to severe ARDS in whom the Pplat exceeds 28 cm H\(_2\)O in the absence of reduced chest wall compliance. Subsequent to the PALIICC publication, Bateman et al. reported in a secondary analysis of data from the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial that early HFOV use for pediatric ARDS was associated with a longer duration of mechanical ventilation but without a significant difference in mortality. This study raises the question of whether HFOV per se led to the longer length of ventilation or whether the issue is the current approach to the management of HFOV. Until a randomized, controlled trial is performed in the pediatric ARDS population, the use of HFOV in pediatrics will likely continue to be debated.

**Adjunctive Therapies**

**Prone Positioning**

ARDS is a disease characterized by heterogeneous lung parenchyma, with the majority of patients having a vertical and anatomic ventilation gradient with decreasing ventilation both in the nondependent-to-dependent axis and in the cephalad-to-caudad axis. Studies have demonstrated that up to 70% of patients with ARDS placed in the prone position have improvements in oxygenation with this
intervention. Proposed explanations for this phenomenon include increased end-expiratory lung volume, better ventilation-perfusion matching, improved regional ventilation, and less compressive effect of the mass of the heart on the lower lobes. However, multiple previous randomized trials and meta-analyses failed to consistently show an improvement in mortality with prone positioning.

In a 2013 multicenter, randomized, controlled trial (Proning Severe ARDS Patients [PROSEVA]) of patients with early (less than 36 hours), moderate to severe (P/F < 150 mm Hg) ARDS, 466 subjects were assigned to undergo prone positioning for at least 16 hours per day versus remaining supine throughout their course. Both groups received a lung-protective ventilation strategy, and standard ICU beds were used for all patients. Prone treatment was stopped based on improvements in oxygenation and/or complications that occurred during prone positioning that necessitated immediate stoppage. The groups were well matched at baseline. Twenty-eight-day mortality was 16.0% in the prone group and 32.8% in the supine group (p < 0.001), with a hazard ratio of 0.39. Similar improvements in mortality were noted at 90 days. Patients in the prone group were extubated sooner and had more ventilator-free days than those in the supine group. Importantly, rates of adverse events such as unintended extubation or removal of catheters were similar in the two groups, with the supine arm actually having an increased rate of cardiac arrest compared with the prone arm. Potential explanations for the unprecedented mortality benefit in this study include selection of sicker patients, a threshold effect of longer prone positioning duration per day, and the use of prone positioning as an early intervention instead of a rescue therapy. Based on this trial and the physiologic rationale for its use, prone positioning should be strongly considered in patients with severe, early ARDS, particularly in those with significant heterogeneity of lung involvement.

The situation for prone positioning for pediatric ARDS is less clear. In 2005, Curley et al published a randomized, controlled trial of prone positioning for infants and children with acute lung injury. The study was stopped at a planned interim analysis due to futility. It should be noted that the degree of ARDS was less in the Curley study than in the PROSEVA trial. PALICC stated that prone positioning cannot be recommended as routine therapy for children with ARDS; however, it should be considered as an option for pediatric patients with severe ARDS. Further study is clearly needed for pediatric ARDS.

**Neuromuscular Blockade**

NMB can be used in the care of adult and pediatric patients with severe hypoxemia and ARDS, particularly those who continue to exhibit signs of ventilator-patient dyssynchrony despite appropriate pharmacologic sedation and appropriate ventilatory management. In a multicenter, randomized, controlled trial, 340 adult subjects with moderate to severe ARDS (P/F < 150 mm Hg), with ARDS onset within the previous 48 hours, were randomized to receive 48 hours of NMB with cisatracurium versus placebo. Open-label boluses of cisatracurium were allowed in both arms in response to high end-expiratory Pplats. Lung-protective ventilation strategies were used for both groups.

While the study was underpowered, the hazard ratio for death at 90 days in the cisatracurium group was 0.68 (95% CI, 0.48–0.98; p = 0.04) after adjustment for
severity of illness. Crude mortality at 90 days was 31.6% in the NMB group versus 40.7% in the placebo group ($p = 0.08$). Mortality at 28 days was 23.7% in the NMB group versus 33.3% in the placebo group ($p = 0.05$). Ventilator-free days, ICU-free days, and rates of barotrauma were also lower in the cisatracurium arm. Equally important, rates of ICU-acquired paresis, felt to be a significant risk in the use of NMB and known to contribute to long-term ICU outcomes, was similar between the two arms despite the high infusion rate and cumulative dose of cisatracurium administered. A replication study powered to confirm the mortality benefit is currently underway as part of the Prevention and Early Treatment of Acute Lung Injury (PETAL) network.

There are many potential explanations for the benefit of NMB in the ARDS population. Pharmacologic paralysis ensures more accurate ventilator mechanics measurements, thereby possibly adjusting settings that cause regional overdistention and/or cyclic alveolar collapse. Specifically, in patients who are dyssynchronous or even making spontaneous breath efforts in concert with the ventilator, pleural pressure may be significantly negative and transpulmonary pressure therefore unexpectedly high. Lower circulating cytokine levels in the paralysis group supports the theory that prevention of VILI and not improved oxygenation was the mechanism of benefit and suggests a reduction in systemic inflammation, or biotrauma. The separation in the survival curves in this study also occurred relatively late in patients’ course, implying that the benefit may be caused by the prevention of biotrauma and subsequent multisystem organ failure. Lastly, reduced oxygen demand by skeletal muscle may also play a role. Although the mechanism for benefit of NMB remains speculative, early administration of cisatracurium is recommended in adult patients with severe ARDS, especially if there is evidence of ventilator-patient dyssynchrony despite deep adequate sedation.

Because there has not been a randomized, controlled trial of NMB in pediatrics, a definitive statement is not possible. PALICC recommended that, if sedation alone is not adequate to achieve “effective mechanical ventilation,” NMB should be considered. Without more definitive data, the pediatric intensivist is again left with relying on expert opinion, such as PALICC, or extrapolating the available data from the adult population.

**Noninvasive Ventilation and Oxygenation**

Studies have examined the role of noninvasive positive pressure ventilation (NIV) in patients with acute respiratory failure with the goal of avoiding intubation and the risks associated with invasive positive pressure ventilation. Positive results were seen for adults with cardiogenic pulmonary edema and chronic obstructive pulmonary disease. However, studies have failed to demonstrate a benefit of noninvasive ventilation for those with other causes of respiratory failure, such as pneumonia or ARDS.

More recently, high-flow nasal cannula (HFNC) with heated/humidified gas flow of > 30 L/min has been proposed as a treatment for patients with non-hypercapnic acute hypoxemic respiratory failure that cannot be reversed with lower oxygen flows. In a cohort of adult patients with non-cardiogenic acute hypoxic respiratory failure ($P/F < 300$ mm Hg), more than 75% of whom had bilateral pulmonary infiltrates, subjects were randomized equally to HFNC, NIV, or standard oxygen therapy delivered.
through a mask. The primary outcome was the rate of intubation at 28 days. In the overall study population, there was no significant difference in rates of intubation between the three groups ($p = 0.18$ for all comparisons). However, in a subgroup analysis of those with P/F < 200 mm Hg, intubation rates were lower in those who received HFNC. More ventilator-free days were seen in the HFNC group, and the hazard ratio for death at 90 days favored HFNC as compared with NIV or standard oxygen therapy.

While HFNC is unlikely to have a significant impact on Vts, NIV uses applied inspiratory and expiratory pressure, which can have a significant effect on Vts and increase the risk for VILI, especially in patients with preserved respiratory drive. This may be especially important in the early phase of ARDS. In a prospective multisite cohort study of adult ARDS patients, investigators studied the association of ICU mortality both with initial Vt during mechanical ventilation and with Vt change over time. Approximately two-thirds of subjects had initial Vts greater than 6.5 mL/kg IBW. They found that an increase of 1 mL/kg IBW in initial Vt conferred a 23% increase in ICU mortality risk (adjusted hazard ratio 1.23, $p = 0.008$). Additionally, a subsequent increase in Vt of 1 mL/kg IBW beyond the initial Vt was associated with a 15% increase in mortality risk (adjusted hazard ratio 1.15, $p = 0.019$). This study further stresses the importance of timely initiation of lung-protective ventilation in ARDS patients to prevent VILI, regardless of whether the positive pressure is applied invasively or noninvasively. Therapies such as NIV and HFNC may contribute to VILI because of the inability to accurately predict or control Vts. This risk must be balanced against the risks of invasive mechanical ventilation. Additional studies are needed to determine the roles of NIV and HFNC in both the adult and pediatric ARDS populations.

**KEY POINTS**

- ARDS is a clinical syndrome defined by the acute onset of bilateral pulmonary infiltrates and hypoxemia not attributable to cardiogenic pulmonary edema.
- Despite being well studied in the adult population, the only management approach that has been shown to improve outcomes is low tidal volume ventilation.
- Other approaches with supportive data for those with severe ARDS include prone positioning and neuromuscular blockade.
- In pediatrics, definitive data are lacking. Clinicians are often left with expert opinion, such as the Pediatric Acute Lung Injury and Consensus Conference (PALICC), and/or extrapolation of data from the adult ARDS population.

**REFERENCES**


CARDIOPULMONARY INTERACTIONS

John J. Marini, MD, and Parthak Prodhan, MD, FCCM

**Objective**

- To describe and illustrate by case examples the basic principles of respiratory mechanics and hemodynamic behavior that determine cardiopulmonary interactions during mechanical ventilation in critically ill adult and pediatric patients

**INTRODUCTION**

The cardiovascular and respiratory systems are tightly interdependent in delivering adequate quantities of oxygenated blood to vital organs at acceptable biologic cost. This chapter outlines the fundamental consequences of lung inflation on cardiac performance and describes key interactions that occur between the lungs and heart during mechanical ventilation of patients with cardiorespiratory failure. The discussion will first describe the physiologic basis of cardiopulmonary interaction and then demonstrate how important physiologic principles are brought to bear on common important conditions faced by practitioners during support of the integrated cardiorespiratory system.

**ESSENTIAL CONCEPTS**

As bioelastic structures, the heart, lungs, and chest wall share the inherent ability to oppose a distending force and then to return to resting or unstressed volume after the force has been removed. The lungs envelop the pericardium and are themselves enclosed within the chest wall. During the tidal cycle, the lungs undergo much greater volume changes than does the heart. Consequently, respiratory events have a much greater effect on the heart than the heart has on the mechanics of the lungs and chest wall. When considering the impact of respiratory events on hemodynamics, several fundamental principles must be kept in mind.

**Transmural Pressure**

For any passive but flexible structure with elastic properties, expansion is determined by the net force applied across it. Therefore, the volume change that occurs in response to any increment of measured internal pressure is determined by the increment of surrounding external pressure. The difference between inside and outside pressures is termed transmural pressure or, in the case of the lungs, transpulmonary pressure.\(^1\) A mechanical ventilator generates positive pressure relative to atmosphere. Static (stop flow) circuit pressures distribute across the lung and chest wall according to their relative elastic properties, as they are arranged in series. Therefore, the impact on lung volume of positive end-expiratory pressure
PEEP), plateau pressure, and their difference (known as the driving pressure) is determined in conjunction with the pleural pressure that surrounds it. The same is true of the pulmonary vessels and the heart during its relaxation phase. Lung compliance, the volume change that occurs in response to a unit of applied transpulmonary pressure, is influenced not only by the mechanical properties of the tissue itself but also by the number of lung units available to accept the additional air volume. The chest wall undergoes an identical volume change as that experienced by the lung, but under passive conditions transmural expanding force is the increment of pleural pressure alone.

The heart and blood vessels must be considered from a similar perspective. It is the volume change that corresponds to transmural pressure, not to vascular pressure alone that determines cardiac fiber stretching. More precisely, the wall stresses that determine preload and afterload relate also to chamber radius and wall thickness, in keeping with LaPlace’s Law: wall stress = \( \frac{\text{transmural pressure} \times \text{radius}}{2 \times \text{wall thickness}} \). The heart, enclosed by the lungs, is exposed to the pleural pressure changes of tidal respiration, which act as the “outside” pressures that oppose or aid the internal pressure to distend or empty the cardiac chambers. Thus, the transmural pressure of the heart can be considered as the pressure within the lumen minus the pericardial pressure, which in most instances is equivalent to pleural pressure. Unlike the lung, the cardiac ventricles can be considered passive only during the diastolic (filling) phase of their cycle.

During spontaneous breathing, the muscles generate negative pressure surrounding the passive lungs, which creates the pressure differential that allows air to flow into the alveoli. In this circumstance, the inflating pressure clearly cannot be judged simply from the change in airway pressure, but requires an estimate of the intrapleural pressure swing as well. In the clinical setting this estimation can be accomplished by using an esophageal balloon catheter to approximate the pleural component. In fact, the distending and driving pressures of the lung itself are best evaluated clinically using the airway minus esophageal (transmural) pressure, whatever the activity or passivity of the muscular pump. This is especially advisable when the chest wall is not compliant or when vigorous efforts occur during spontaneous or machine-assisted breathing.

**Determinants of Cardiac Output**

Like the lungs, the heart in diastole behaves as a structure that expands according to the transmural pressure and the chamber-specific elastic properties. (Flexibility is quantified by compliance, and stiffness by the inverse, termed elastance.) In systole, fiber shortening and ejection are determined in part by contractility and partly by opposition from the transmural pressures of afterload. These characteristics are described in the classic and familiar Frank-Starling curves that relate filling pressure (transmural end-diastolic pressure) to stroke volume or stroke work. It is important to recognize that afterload sensitivity of the normal right ventricle is much greater than that of the left, whereas its thickness and contractile power are much less. The right ventricle fills passively through much of its range, only demonstrating true elastic properties when it becomes quite distended. Thus, the Starling curve of the right ventricle rises steeply and plateaus quickly in comparison to its left-sided counterpart.
Importance of Venous Return

In practice, the forward output of the heart is determined not only by Starling characteristics, but also by the forces that return venous blood back to the heart. Blood is circulated by pressure differentials; it is the task of the left heart to generate a mean systemic arterial pressure sufficiently higher than the central venous pressure (CVP) to overcome the resistance of the intervening vascular network. A large part of the vasculature of the normal systemic network serves as a capacitance bed, filling and contracting as needed to maintain an adequate upstream pressure to power venous return. The average pressure in the systemic vascular circuit is known as mean systemic pressure (MSP), which lies much closer in value to the venous pressure than to the arterial pressure, owing to the relatively extensive venous reservoir. Venous return is driven by the difference between MSP and right atrial pressure. That pressure differential dissipates against the intervening venous resistance, which generally is quite small. According to principles popularized by Guyton, cardiac output can be viewed as the intersection between the Starling curve that describes systolic cardiac behavior, and the venous return curve drawn by a plot of venous return against right atrial pressure. Both the cardiac and the venous flow relationships must be satisfied within this closed hemodynamic circuit.

Mean Airway Pressure and PEEP

Another concept key to the understanding of heart-lung interactions during mechanical ventilation is that of mean airway pressure. During controlled mechanical ventilation of a passive patient, all work of ventilation is performed by the machine-generated pressure and gas flow during the inflation phase, and stored potential energy dissipates across airway resistance during exhalation, driven by alveolar minus central airway pressure. When inspiratory and expiratory resistance losses of energy are equivalent, pressure averaged across the entire respiratory cycle must be the same throughout the airway, including the alveoli. Therefore mean airway pressure measured at the airway opening and recorded in the ventilator circuit approximates mean alveolar pressure quite well, except when expiratory pressure losses exceed those during inspiration, as in diseases of airflow obstruction. Under such circumstances mean alveolar pressure is often augmented by dynamic hyperinflation caused by auto-PEEP. Mean airway pressure can be increased by raising PEEP, prolonging the duty cycle (increasing the I:E ratio), or increasing the driving pressure, which is the quotient of tidal volume and respiratory system compliance. A primary and powerful—but not unique—component of mean airway pressure is the baseline from which inflation begins, ie, PEEP. Because increasing minute ventilation requires more driving pressure, a shorter frequency-determined expiratory time, or both, increasing minute ventilation directly influences mean airway and alveolar pressures, even when auto PEEP is not generated. Mean airway pressure is important to the operating characteristics of the heart and circulation because it influences the pleural pressure that surrounds the heart. Under passive conditions, higher mean airway pressure results in larger average lung size and chest wall dimensions, and therefore correlates with higher values for pulmonary vascular resistance (PVR), pleural pressure, and back pressure to venous return. Despite their implications, it must be emphasized that these key physiologic correlations of mean airway pressure and hemodynamics do not apply during spontaneous efforts.
Dynamic Effects of Respiration on Cardiovascular Function

Inflation of the lung by positive pressure increases PVR and raises pleural pressure, thereby imposing a back pressure to venous return (Figure 1). The latter effect contrasts with the reduced venous back pressure encountered during spontaneous breathing.

Figure 1. Inflation of the lung by positive pressure

As the lung is inflated by positive pressure, rising pleural pressure increases the external pressure on the great vessels and imposes a back pressure to venous return. Simultaneously, the inflated lung (here by 20 cm H₂O alveolar pressure) increases PVR. At high lung volumes, the pericardium may be significantly compressed, and the inferior vena cava may narrow at the thoracic inlet (arrows).

Effects of Respiration on Right Ventricular Preload

As the lung is inflated by the ventilator alone, by spontaneous breathing alone, or in the varied combinations of partially assisted breathing, changes occur in the transmural pressures that determine preloading and afterloading conditions of the right ventricle and in the abdominal pressures that help determine the upstream driving pressure for venous return. Normally, the abdomen is the most compliant portion of the chest wall, so that as the diaphragm descends and the ribs expand during inflation, abdominal pressure rises to some degree. (Phasic changes in abdominal pressure that occur during the tidal cycle can be monitored with the use of bladder pressure.\textsuperscript{8}) Under controlled conditions, this rise of abdominal pressure tends to boost MSP, but unless the right ventricle operates near its upper Starling plateau, the rise in MSP is insufficient to compensate for the even greater rise in right atrial pressure. If MSP is not boosted by contracting the capacitance bed, venous return will fall. Release of the positive airway pressure reverses the sequence. During passive ventilation (as opposed to assisted or spontaneous breathing), the resulting amplitude of tidal variations in systolic and pulse pressure tends to correlate with the responsiveness to intravenous fluid loading, particularly when large tidal volumes are in use.\textsuperscript{9} Conversely, during spontaneous inspiration, the muscle-powered descent of the diaphragm raises abdominal pressure and MSP while reducing the back pressure to venous return, improving the venous return.
gradient. On average, the gradient for venous return is higher during spontaneous breathing than during controlled ventilation, an advantage that is accentuated when the circulation is underfilled. Consequently, the circulatory disadvantage of undertaking controlled ventilation is accentuated when the patient is relatively dehydrated or vasodilated. Increases of mean airway pressure caused by increases of PEEP or minute ventilation accentuate the disparity between spontaneous and positive pressure breathing. In this context it should be noted that right atrial pressure may rise because of decompensation of the right ventricle, rather than from its underfilling. Thus, when inflation causes an undue rise in right ventricular afterload, right atrial pressure may rise sufficiently to impede venous return, adding to any impediment to right ventricular ejection caused by higher PVR.

Overdistention of the right ventricle impairs compliance of the left ventricle made interdependent with it by circumferential muscle fibers common to both and by their shared intraventricular septum and pericardial space (Figure 2). Extreme overfilling of the right ventricle may also compromise the perfusion of its own thin myocardium, encouraging contractile dysfunction.

Figure 2. Schematic cross-sectional view of the ventricles

Schematic cross-sectional view of the ventricles showing the crescent shape of the right ventricle juxtaposed to the left ventricle, with the muscle fibers in the interventricular septum being shared between the chambers (A). A major acute change in pressure within the right ventricle can cause a shift in septal position (often resulting in a so-called a D-shaped septum), contributing to forces that reduce the compliance of the left ventricle (B).

Effects of Respiration on Right Ventricular Afterload

The right ventricle has limited capacity to generate pressure against PVR. PVR is powerfully influenced by reduction in the number of patent capillaries due to disease, atelectasis, alveolar overdistention, and by vasoconstriction caused by hypoxia, acidosis, and certain drugs. When the capillary reserve is compromised by extensive disease, lung distention resulting from ventilatory support with positive pressure accentuates PVR and can challenge the ability of the right ventricle to compensate. During inflation, alveolar capillaries are compressed, and extra alveolar vessels dilate. The former effect dominates the latter so that PVR usually rises as a monotonic function of airway pressure (Figure 3). However, in the specific setting of acute lung injury and pulmonary edema, PEEP may recruit sufficient volume and bring new capillaries online to offset its simultaneous detrimental impact on alveolar
capillary compression. Once the capillary bed approaches full recruitment, high mean airway pressure may redirect a portion of the pulmonary blood flow through consolidated lung regions or prompt right-to-left shunting through a patent foramen ovale. When lung tissue is normal, the adequately filled right ventricle can usually compensate for quite high levels of mean alveolar pressure. However, when the capillary bed is restricted, considerably lower levels of PEEP and mean airway pressure may exceed tolerance. The resulting increases of right ventricular and right atrial pressure may also force open a patent foramen ovale, contributing to systemic hypoxemia.

**Figure 3.** Schematic relationship of lung volumes and pulmonary vascular resistance (PVR)

![Diagram of lung volumes and pulmonary vascular resistance]

PVR is lowest at functional residual capacity. It increases with lung hyperinflation (due to increased alveolar vascular resistance) and with low lung volumes (due to increased extra-alveolar vascular resistance).

**Pediatric Considerations**

The physiologic principles detailed earlier in this chapter apply to children as well as adults. Among infants and children, the developmental immaturity of the cardiorespiratory system lowers and limits functional reserve. In the face of respiratory and/or cardiac disease, this limited ability to handle stress accentuates adverse cardiopulmonary interaction.

Compared to adults, the respiratory system in children is characterized by a highly compliant chest wall, predominantly diaphragmatic breathing mechanics, horizontal orientation of the rib cage, poor chest recoil, and higher airway resistance. Because of these limitations, there is a tendency for paradoxical inward rib cage motion during spontaneous inspiration, with increased work of breathing, higher
probability for lung collapse promoted by low functional residual capacity, and high resistive loading of the respiratory system. All of these factors, coupled with the higher oxygen consumption in infants (6-8 mL/kg/min) compared to adults (3-4 mL/kg/min) place neonates and infants at higher risk of respiratory decompensation and adverse effects of ventilatory support.

Similarly, the neonatal myocardium differs significantly from the adult myocardium in its intrinsic structure and function. The cellular differences in myocardial fiber arrangement, the amount of fibrous tissue and immaturity of the sarcoplasmic reticulum impede myocardial relaxation. In the face of stiff myocardium, limited inotropic reserve and reduced preload capacity, neonates mount an increased heart rate response to augment cardiac output. In this setting, any increase in afterload is more likely to produce a significant drop in cardiac output than it would in older children and adults. As the child grows, there is functional maturation as the myocardium adapts progressively to its new loading conditions and develops increased responsiveness to beta receptor-stimulation. During this period of growth, the heart morphology changes as well. The left ventricle in neonates is nonconcentric and the interventricular septum is coupled to the right ventricle instead of the left ventricle. In older children the septum is recruited by the left ventricle and makes the left ventricle become more concentric, as in adults.

Due to these functional considerations, neonates and infants with impaired cardiac function encounter relatively greater effects regarding transmural cardiac pressure in response to changes in intrathoracic pressure than do adolescents and adults. This sensitivity is accentuated by the lower blood pressure ranges in neonates and infants compared with their older counterparts.

Children with a functional single ventricle who undergo the Fontan palliation procedure and those with tetralogy of Fallot are especially sensitive to increases of intrathoracic pressure. After the Fontan procedure, the superior and inferior venae cavae are connected to the pulmonary artery without an intervening subpulmonary pumping chamber to overcome the resistance of the pulmonary circulation. For these reasons, the effects of changes in intrapleural pressure on venous return and ventricular filling predominate over those effects on the afterload of the systemic ventricle. Any increase in intrathoracic pressure in these patients profoundly decreases cardiac output, and they benefit greatly from ventilatory strategies that decrease end-expiratory, peak and mean airway pressures. Intrathoracic pressure is also minimized by optimizing delivered tidal volumes, using relatively short inspiratory times, and avoiding rapid ventilator rates that produce dynamic hyperinflation and auto-PEEP. For a similar reason, increases of intrathoracic pressure tend to impressively impair preload in patients with right ventricular dysfunction after repair of tetralogy of Fallot.

CASE EXAMPLES

**Cardiopulmonary Interactions in Acute Severe Asthma**

**Case Description:** An otherwise healthy 19-year-old man presents with an acute exacerbation of asthma for the past 12 hours. He has not responded well to his albuterol inhaler or inhaled steroids and has become increasingly dyspneic. On arrival at the emergency department, he can barely speak in two- to three-word
phrases. From a tripod position, he is in severe respiratory distress, making extensive use of all accessory muscles of respiration. Diminished air movement and faint inspiratory and expiratory wheezes are heard throughout both lung fields. His peak flow is severely reduced, at one-third the normal for age. Chest radiograph demonstrates hyperinflated lungs with a normal cardiac silhouette and symmetrically increased markings but no infiltrates. Basic laboratory test results are within normal limits. Despite continuously nebulized albuterol solution and 60 mg of oral prednisone, respiratory status worsens and remains refractory to intravenous magnesium sulfate, subcutaneous epinephrine, and intravenous methylprednisolone. His arterial blood gases at this time demonstrate a pH of 7.32, Pco\textsubscript{2} of 50 mm Hg, and Sao\textsubscript{2} of 96% with a F\textsubscript{I}O\textsubscript{2} of 40% delivered by facemask. He was therefore urgently sedated, paralyzed, intubated and admitted to the intensive care unit. He remained difficult to ventilate, with very high peak airway pressures (greater than 80 cm H\textsubscript{2}O) in the flow-controlled volume-targeted mode applied with a decelerating waveform. Hypotension abruptly followed the initiation of controlled positive pressure ventilation, and a 1-liter bolus of saline was given. Several ventilatory adjustments were attempted without notable change in his condition. Hypotension eventually resolved with a reduction of breathing frequency and the adoption of permissive hypercapnia. Auto-PEEP, initially measured by end-expiratory occlusion to be 22 cm H\textsubscript{2}O, abruptly fell, along with plateau pressure by 10 cm H\textsubscript{2}O at the lower minute ventilation. He continued to receive nebulized bronchodilators. A ketamine infusion, airway humidification, and intravenous magnesium were added to the other bronchodilating medications while he was kept well sedated. Airway resistance, auto-PEEP and peak airway pressures fell gradually over the next 24 hours, with steadily improving gas exchange. He was extubated successfully on hospital day three and discharged to home on hospital day five.

**Interpretation:** Airway narrowing due to bronchoconstriction, airway edema, thickened mucus, flow limitation and hyperinflation are hallmarks of acute severe asthma. In the setting of low expiratory flow rates, the entire inspired gas volume, which is normally exhaled passively, now requires active exhalation and relatively long expiratory times. However, if the next breath interrupts exhalation, progressive gas trapping occurs. This failure of the lung to return to its relaxed volume or functional residual capacity at end-exhalation is called *dynamic hyperinflation*. Because gas is trapped in the lungs, there is additional alveolar pressure at the end of expiration (auto-PEEP or intrinsic PEEP). Changes in airway properties (eg, increased spasm or mucus) promote gas trapping that works against applied inspiratory pressure. Therefore, pressure-targeted modes of ventilation are risky and, if used, must be closely monitored for their effectiveness in maintaining effective tidal volume and minute ventilation. Flow-controlled, volume-cycled modes, such as used in this case, maintain tidal volume in response to worsened impedance, albeit at the cost of added airway pressure and dynamic hyperinflation.

Dynamic hyperinflation, although necessary to generate the recoil needed to accomplish the tidal volume in the expiratory time available, has highly unfavorable effects on respiratory mechanics and represents a key target for treatment. The elevated pressure gradient that drives expiratory flow must first be reversed before inspiration can begin. Moreover, operating at a higher position on the pressure-volume relationship impairs compliance of the respiratory system and markedly increases the elastic work of breathing (Figure 4). It also flattens the
diaphragm (imposing a geometric disadvantage to its descent), thereby reducing force-generating capacity, since muscle contraction starts from a mechanically disadvantageous fiber length. 

**Figure 4.** Schematic inflation pressure volume curve

---

Schematic inflation pressure volume curve for a normal subject and for one with severe airflow obstruction who take identical tidal volumes. Auto-PEEP (AP) and reduced compliance add significantly to the inflation work of breathing (shaded areas). Auto-PEEP raises end-expiratory intrathoracic pressure (dashed line) and distends the lung at higher volumes, thereby increasing PVR.

The airways of acutely exacerbated asthma are often extensively plugged, and are quite unlike those of chronic obstructive pulmonary disease, a condition in which the addition of PEEP downstream from the zone of flow limitation narrows the alveolar to airway opening pressure gradient, reducing the triggering threshold for inflation and lowers the work of breathing. Dynamic hyperinflation increases dead space, thus further increasing the minute volume required to maintain adequate ventilation. In short, asthma increases respiratory system load and work of breathing due to its effects on all three of its components, namely respiratory components, resistance, elastance and minute volume, in both the inspiratory and expiratory phases of the tidal cycle.

Another important consequence of airway narrowing is the necessity for excessively negative pleural pressures during inspiration in an attempt to overcome airway obstruction. In alert, spontaneously breathing patients with severe asthma, ventilatory drive is characteristically high. The pleural pressure becomes more negative with increasing disease severity, such that negative intrapleural pressures as low as −35 cm H₂O can be seen during unassisted tidal breathing. Perivascular lung edema and tidally phasic loading of the right and left ventricles promote pulsus
paradoxus on arterial and pulse oximetry tracings. These occur because rapid right ventricular filling during inspiration shifts the interventricular septum toward the left ventricle, causing left ventricular diastolic dysfunction and incomplete filling via ventricular septal interdependence. This process is further worsened by the increase in right ventricular afterload due to hypoxic pulmonary vasoconstriction, acidosis, and increased lung volume. In the setting of decreasing left ventricular preload, the excessively negative intrapleural pressure generated during inspiration also increases left ventricular afterload by elevating systolic transmural pressure. Impaired systolic emptying often ensues. The accentuation of the normal inspiratory reduction in left ventricular stroke volume and systolic pressure leads to the appearance of pulsus paradoxus. The excessive negative pleural pressure also favors transcapillary filtration of edema fluid into airspaces, which can be further worsened by aggressive fluid resuscitation that increases microvascular hydrostatic pressure.

The institution of positive-pressure ventilation in the asthmatic patient dramatically alters cardiovascular and respiratory dynamics. With intubation, pleural pressures suddenly change from predominantly negative to positive, along with quieted respiratory effort and worsening of dynamic hyperinflation. Such dramatic shifts can cause life-threatening complications such as hypotension, oxygen desaturation, air leak syndromes, and cardiac arrest during the peri-intubation period. Excessive gas trapping due to PPV diminishes venous return, causing hypotension, which is worsened by the vasodilatory and myocardial depressant effects of sedatives and paralytics. Post-intubation hypotension often responds to volume loading and slowing of the ventilatory rate.

Close attention to the basic principles of ventilating patients with severe asthma is crucial for a favorable outcome: employ low tidal volumes and respiratory rate, adopt permissive hypercapnia, prolong expiratory time, and monitor for the development of dynamic hyperinflation. Note that, while moderately high flow settings are appropriate, very high inspiratory flow rates can be counterproductive, as the marginally longer expiratory time helps little in decompressing the chest, while faster inspiratory flows require higher airway pressure and promote heterogeneity of ventilation and tissue stretch. Reducing ventilation demands and maintaining patient-ventilatory synchrony are more important than micromanaging the fine details of the ventilator settings.

**Cardiopulmonary Interaction in Patients with Congestive Heart Failure**

**Case Description:** A 63-year-old woman weighing 75 kg presents with progressively worsening shortness of breath, anorexia, orthopnea, and dysuria over the past week. Laboratory data indicate modest leukocytosis and urinary tract infection. Her past medical history is significant for two myocardial infarctions, hypertension, non-insulin dependent diabetes, and a lifelong habit of cigarette smoking. Her outpatient medications include atenolol and lisinopril. Physical examination reveals an undernourished woman with labored breathing. Vital signs are: blood pressure 170/110 mm Hg in the right arm, heart rate 96 beats/min, respiratory rate 26 breaths/min, temperature 38.5°C. Coarse rhonchi, faint wheezes and moist, inspiratory crackles are heard bilaterally in the lower lung fields. Neck veins are distended to the mandible when she is sitting upright. An S3 gallop and grade 3/6 holosystolic murmur are audible over the precordium. There is a diminished and
irregular pulse and pitting edema of both lower extremities. Complete blood count is normal. Blood urea nitrogen and creatinine tests indicate prerenal azotemia. N-terminal brain natriuretic acid is three times the upper limit of normal. The chest radiograph reveals moderate cardiac enlargement and lung fields that are compatible with acute congestive heart failure. Arterial blood gases and electrolytes indicate mixed metabolic and respiratory acidosis. Electrocardiogram demonstrates T-wave inversions that indicate ischemic changes and frequent premature ventricular contractions. Echocardiogram shows biventricular enlargement and an ejection fraction of 25%. Aggressive diuresis and noninvasive PPV (20/10 cm H₂O) with supplemental oxygen are initiated, antibiotics are given and beta-blockers are withheld, with relief of dyspnea and ensuing improvement in clinical status and blood gases over the following 24 hours.

**Interpretation**: This patient appears to have elements of systolic as well as diastolic heart failure, perhaps made worse by chronic beta blockade. Although useful in the chronic setting to limit heart rate, prevent ischemia, and lower blood pressure, beta-blockers narrow the heart's physiologic reserve under conditions of stress. Not only do they impair contractility and limit compensatory heart rate response, they impair edema clearance, promote bronchospasm and marginally increase left ventricular afterload. The oxygen demands, work of breathing, loading conditions of the heart and pulmonary gas exchange were all improved by the application of PPV. In patients with acute cardiogenic pulmonary edema, conversion from fully spontaneous breathing to assisted PPV usually confers multiple benefits. During unsupported respiratory distress, the workloads of the cardiac and the respiratory muscle pumps are both increased, and the loading conditions of the left ventricle are compromised by the strongly negative pressure that surrounds it during inflation. During overt heart failure, the myocardium may stiffen (especially when heart rate rises) and contractile function worsens in response to its excessive burden, in particular when ischemia and/or functional mitral valve dysfunction develop, as in this case. Moreover, increased CVP swells the right ventricle and impairs left ventricular compliance by interdependence effects. Edema that forms in the lung not only worsens oxygen exchange but causes cardiac asthma due to swelling of the small airway linings and/or vagal receptor stimulation. (Residual beta blockade does not help with fluid of secretion clearance or bronchospasm.) Under conditions of labored breathing caused by cardiac failure, the diaphragm and respiratory muscles may be called upon to perform an unsustainable workload while receiving an inadequate flow of oxygenated blood, contributing to cardiorespiratory decompensation. 

A prudent ventilation strategy is to reduce oxygen consumption by taking over a substantial portion of the breathing workload, to minimize the amplitude of negative inspiratory pressures by pressurizing the airway, and to use continuous positive airway pressure (CPAP) to improve pulmonary gas exchange and reduce venous congestion within the central veins. In many instances, providing inspiratory assistance with pressure support is important, but elevating the end-expiratory pressure baseline is key to success; CPAP alone may be all that is required to unwind the downward spiral of cardiorespiratory decompensation. In the patient with preserved ventilatory drive, as in those (like this patient) who are given ventilatory support noninvasively by mask, the use of PEEP very rarely causes a detrimental reduction in cardiac output. However, when systemic vasodilation occurs, as when nitrates, opiates and deep sedation are used, the patient becomes more vulnerable to impeded venous return. This vulnerability often becomes overt shortly after
intubation, when all respiratory power is provided by positive pressure and the pumping actions of spontaneous breathing are silenced.

These principles of managing heart-lung interactions hold up equally well after the acute phase of illness is over and aggressive support is being withdrawn. In vulnerable patients with diastolic, systolic and valvular problems—known or occult—resuming spontaneous breathing reverts the heart and often contributes to failure to accomplish ventilator independence (“liberation” or “weaning”). Suddenly shifting from a positive to a negative intrathoracic pressure results, on the one hand, in an increased pressure gradient for systemic venous return and in cardiac preload. On the other hand, such shifts impede left ventricular ejection and increase left ventricular afterload. In patients with previously impaired left heart function, both mechanisms hold potential to increase central blood volume and eventually lung filtration pressure. In some conditions, the stress of resuming spontaneous breathing may increase right ventricular afterload and enlargement, raising left ventricular end-diastolic pressure through diastolic interdependence. Finally, in patients with prior coronary artery disease or ventricular thickening, myocardial ischemia and diastolic dysfunction may be provoked by the imposed breathing workload. In carefully selected cases, early use of CPAP or bilevel positive airway pressure (BiPAP) in conjunction with diuretics and anti-ischemic therapies (nitrates, mild sedation, and analgesia) may forestall or prevent the need for reintubation.

**Cardiopulmonary Interactions in Acute Respiratory Distress Syndrome**

**Case Description:** Ascending cholangitis due to a common bile duct stone develops in a 60-year-old woman with obesity (42 BMI) and diabetes with prior history of hypertension, chronic renal insufficiency, and echo-documented diastolic dysfunction. High fever to 40ºC, hypotension and acidosis are initially accompanied by tachycardia and warm, flushed skin. Lactate is measured at 6 mm/L. Aggressive volume resuscitation, norepinephrine, volume-controlled mechanical ventilation, and antipyretics are begun. Severe acute respiratory distress syndrome (ARDS) develops, and minute ventilation rises to 16 L/min with vigorous spontaneous efforts on BiPap 18/8 cm H₂O. Arterial blood gases are: pH 7.24, Pao₂ 60 mm Hg, Paco₂ 36 mm Hg, Pao₂/FIO₂ 110 despite FIO₂ of 0.90, and PEEP 14 cm H₂O. Phasic variations of systolic and pulse pressures are noted to be synchronous with tidal breaths on the tracing from her radial arterial line. ECG-determined heart rhythm remains sinus, and no Q waves or ST segment changes are observed. Over the first six hours of admission, six liters of crystalloid are administered, and endoscopic retrograde cholangiopancreatography with stone extraction and common bile duct stenting is performed successfully. Although minute ventilation fell to 13 L/min within the first hour of noninvasive ventilation, vigorous spontaneous breathing persists. Intubation is performed, and severe hypoxemia, though marginally better, remains unresolved and unacceptable. Forceful use of the expiratory muscles is noted. A “staircase” recruiting maneuver (using a constant tidal volume and stepwise increments of PEEP) is only transiently effective and is accompanied by short-lived but worrisome hypotension during the maneuver. Raising PEEP to 20 cm H₂O is briefly tried, without benefit, causing a mild decline in blood pressure and worsening of arterial oximetry values. Measured CVP on 14 cm H₂O PEEP is high (22 mm Hg), and mixed venous oxygenation saturation low (30 mm Hg). Systolic PA pressure is estimated from TR jet velocity on Doppler echocardiogram as 45 mm Hg plus RA
pressure. Moderate right ventricular dilation with D-shaped and left shifted interventricular septum are detected. Inhaled prostacyclin is initiated with only marginal benefit to oxygenation. Deeper sedation and paralysis result in disappearance of respiratory variations of systemic arterial pulse pressure and in modest improvement of \( P_{aO_2}/F_{iO_2} \) ratio. These occur without significant change in norepinephrine-supported systemic blood pressure. Bladder pressure is recorded supine as 20 cm H\(_2\)O (14 mm Hg). The decision is made to undertake prone positioning. Shortly after this is accomplished, blood pressure and oxygenation both improve significantly.

**Interpretation:** A key principle of managing cardiopulmonary interactions in a complex case of ARDS such as this one is to optimize right ventricular performance by paying appropriate attention to its ventricular loading conditions. In this case scenario, the elevation of lactate, acidosis, and hypotension are compatible with septic shock, and this is addressed in standard fashion with intravenous fluids, antibiotics, and vasopressors. Antipyretics are controversial, but in this case may help to reduce demand for cardiac output, which in turn should help to reduce hydrostatic filtration across the lungs' leaky blood vessels. In this volume-loaded, obese patient supported by mechanical ventilation, assessing true filling pressures of the ventricles is challenging, as it requires making an assumption regarding intrapleural pressure. Placement of an esophageal balloon catheter (not done here) would have been helpful in this patient with a heavy chest wall, increased abdominal pressure and vigorous breathing, not only to keep true driving pressures across the lungs within acceptable limits, but also to better evaluate the cardiac filling pressures. Bedside ultrasound and echocardiography are invaluable when assessing filling status and ventricular dimensions, as well as pulmonary arterial pressures. Here, the high PA pressure is concerning for several reasons. With the normal capillary bed restricted to less than a third of its normal capacity by disease, hypoxemia, and acidosis, the higher cardiac outputs of distributive shock have caused PA pressure to approach or exceed the adaptive capacity of the normal right ventricle and cannot be sustained for long by the stressed and dysfunctional RV. Elevated right atrial pressures act as a back pressure to venous return and, in a significant minority of patients, high right atrial pressures may also promote shunting through a patent foramen ovale.

The elevated bladder pressure of approximately 15 mm Hg (20 cm H\(_2\)O), recorded here under passive conditions (as it must be), indicates that approximately 7.5 cm H\(_2\)O transmits to the pleural compartment. (Approximately 50% of the measured value for bladder pressure above 5 cm H\(_2\)O—which in this instance is one half of 15 cm H\(_2\)O—can be expected to transmit to the pleural space.) Therefore, adjusted PA and CVP might be expected to be exaggerated by approximately 5 mm Hg (and their transmural pressures overestimated by that amount) owing to the estimated boost in pleural pressure resulting from high intra-abdominal pressure.

Adequacy of cardiac filling and fluid responsiveness can be assessed by respiratory cycle fluctuations of arterial pulse pressures during controlled but not spontaneous or assisted breathing. In this case filling must have been more than adequate, since respiratory fluctuations disappeared once breathing efforts were silenced, and blood pressure did not deteriorate significantly after muscle relaxation, even though the gradient for venous return likely became less after quieting the thoraco-abdominal
pump for venous return. Indeed, the D-shaped and left-shifted septum indicate that the right heart was at risk for acute cor pulmonale, a condition in which further fluid volume loading may be ineffective or even counterproductive.

Acute cor pulmonale was developing because the right heart had been put under unacceptable strain by increased PVR. Though inhaled prostacyclin was a reasonable intervention to try, it did not work well, and neither did recruiting maneuvers or application of very high PEEP. Once recruitment of collapsed lung units in response to PEEP becomes overshadowed by increased stretch of lung units already open, lung compliance falls and effective PVR rises in response to further PEEP increments. When this happens, blood flow redirects toward less well-ventilated or airless units under the influence of high mean airway pressure. Hypoxemia and dead space may then increase, and the right ventricle is put at risk to decompensate further. Such regional overstretching accounts for the observed hypotension in response to recruiting maneuvers and for the failure of elevating PEEP applied in the supine position to improve oxygenation.

Although proning the patient stiffened the chest wall and likely helped translocate into the thorax some blood from the abdominal capacitance vessels, it likely recruited new lung units and expanded the pulmonary capillary bed, too—even in this obese patient. Just as importantly, proning evened the distribution of transalveolar pressures across the entire lung, reducing regional alveolar overstretch and consequent right ventricular afterload. It is also possible that lower right ventricular wall tension helped improve perfusion and contractile performance of the right ventricle.

**KEY POINTS**

- Transmural rather than intracavitary forces determine the relative distention of the lungs, hydrostatic filtration forces across the pulmonary vasculature, and the loading conditions of the heart chambers.
- The right and left ventricles are interdependent due to shared muscle fibers, septum, and pericardial space.
- Lung distention with positive pressure increases PVR and raises the back pressure to venous return in proportion to the relative stiffness of the lungs and chest wall.
- The major influence of mechanical ventilation on systemic hemodynamics is mediated by altering the loading conditions of the right ventricle.
- Compared to adults, the respiratory system in children is characterized by a highly compliant chest wall, predominantly diaphragmatic breathing mechanics, horizontal orientation of the rib cage, lesser chest recoil, and higher airway resistance. These features accentuate the tendency for lung inflation to influence hemodynamics.
- Cardiopulmonary interactions that occur during mechanical ventilation are especially important to consider in such acute management problems as exacerbated airflow obstruction, heart failure, and noncardiogenic pulmonary edema/ARDS.

**REFERENCES**


OPTIMIZING PATIENT-VENTILATOR SYNCHRONY IN ADULT AND PEDIATRIC POPULATIONs

John D. Davies, MA, RRT, FCCP and Martin C.J. Kneyber, MD, PhD, FCCM

Objectives

- Define patient-ventilator asynchrony (PVA)
- Identify where PVA can occur in a delivered ventilator breath
- Discuss solutions for the different types of PVA
- Discuss two new modes of ventilation that are specifically designed to optimize patient-ventilator synchrony

INTRODUCTION

Monitoring and optimizing patient-ventilator interactions reduces work of breathing (WOB), dyspnea, and stress associated with ventilatory support of the critically ill patient. Recent advances in ventilator technology have yielded the ability to appropriately apply and interpret volume, pressure, and flow waveforms. This enhanced capability, combined with careful observation and physical examination, gives clinicians the tools needed to optimize the interaction between the ventilator and the patient.

Approaches to mechanical ventilation (MV) can be classified as either controlled or assisted. In controlled MV, all parameters of the delivered breath are controlled by the ventilator according to clinician settings. Assisted MV, on the other hand, involves significant interaction between the patient and the ventilator. Thus, the triggering of the breath, flow delivery, and termination of the machine’s inspiratory cycle must match patient demand to avoid asynchrony. The potential for patient-ventilator asynchrony (PVA) exists in three different phases of the delivered breath—triggering of the breath, flow delivery during the breath, and termination of the breath.

CASE STUDY

A clinician is called into an adult patient’s room by the nurse, who says that the patient appears uncomfortable; the nurse wants to sedate him. The clinician agrees with the nurse’s assessment that the patient is uncomfortable. However, on inspecting the ventilator waveforms during flow-controlled, volume-cycled ventilation, the clinician notices that the pressure waveform is being sucked down instead of continuing to rise during the inspiration. The flow and volume tracings appear unaffected. The clinician checks the settings and confirms that the patient is on volume assist-control ventilation. To avoid sedation, what are the options for ventilator settings?

CONVENTIONAL VENTILATOR MODES
Asynchrony in conventional MV can be problematic in that the ventilator will control some of the ventilation parameters—delivered volume, pressure, flow, and timing. More parameters under the control of the ventilator leads to a higher likelihood of PVA. Asynchrony may be subtle or overt; patient distress during PVA is more likely when minute ventilation requirements are high. Conventional modes include volume assist-control ventilation (VACV), pressure assist-control ventilation (PACV), and pressure support ventilation (PSV).

Parameters that are set by the clinician (and are therefore fixed and not controlled by the patient) for a breath delivered in VACV include tidal volume (Vt), flow, and flow pattern (descending ramp, sinusoidal, or constant). The only parameter that the patient can affect is pressure. If any of the clinician-set parameters do not match the patient’s requirements, PVA will occur and will be reflected in the pressure waveform. In PACV, the clinician sets only the delivered pressure, the rate of rise to the targeted pressure value, and inspiratory time. The patient can interact with the ventilator to control flow delivery and, as a result, can vary both flow profile and Vt. PSV is the least controlling of conventional MV modes because only one parameter (apart from rate of rise of pressure) is the pressure target. As a result, the patient can influence Vt, flow delivery, and termination time.

**PATIENT-VENTILATOR ASYNCHRONY**

PVA can be categorized into five types: trigger asynchrony, flow asynchrony, cycling asynchrony, mode asynchrony, and reverse triggering. Trigger asynchrony can further be classified as either delayed triggering, missed triggering, or auto-triggering. Flow asynchrony results when the gas delivery from the ventilator does not match the patient’s neural demand (desired inspiratory pattern). It can take the form of either flow starvation (when the flow delivery is less than the patient desires, resulting in increased WOB) or double breaths (flow and Vt are delivered so fast that the ventilator stacks two separate and immediately sequential breaths). Cycling asynchrony occurs when the patient’s inspiratory time differs from the ventilator inspiratory time. This can take the form of either premature or delayed cycling into exhalation. Mode asynchrony occurs when the mode set on the ventilator induces an asynchronous patient response. This usually occurs in volume synchronized intermittent mandatory ventilation (SIMV) when the patient is not sure whether to expect a flow- or pressure-controlled breath or a pressure-supported one. Reverse triggering is thought to be a form of neuromechanical asynchrony in which, in deeply sedated patients, an untriggered machine cycle induces inspiratory muscle activity while delivering a mandatory breath.

**TRIGGER ASYNCHRONY**

Trigger asynchrony occurs when there is miscommunication or no communication between the patient’s muscular effort and the ventilator’s response at breath onset. The machine-triggering criterion can be based on detection of an inspiratory pressure or flow deflection of a magnitude selected by the clinician. The work of triggering increases when there is a delay in ventilator recognition of effort or, in severe cases, complete disregard of it. These situations, referred to as delayed triggering and missed triggering, respectively, can result from either disease or an insensitive triggering setting on the ventilator. Correctly setting the sensitivity requires patient observation and direct adjustment of the ventilator to minimize delay.
and undue work of triggering.

In adult patients, delayed and missed triggers are often—but not invariably—due to severe weakness, drive suppression, and disorders that produce gas trapping and resultant auto-positive end-expiratory pressure (auto-PEEP), such as chronic obstructive pulmonary disease.\textsuperscript{1-4} Triggering asynchrony is the most common cause of PVA in invasively ventilated pediatric patients, with or without lung injury.\textsuperscript{5} In addition, triggering asynchrony is also very common in patients on noninvasive ventilation, usually due to leaks around the mask interface.

Narrowing of the airways in obstructive disease leads to an increased resistance, which in turn results in slower expiratory flows. In this condition, expiratory times are not sufficient to reach relaxed volume, trapping gas in the lungs. The result is the creation of auto-PEEP. When auto-PEEP is present, the patient must generate negative pressure high enough to overcome the positive alveolar pressure left over in the lungs from the previous exhalation before the circuit pressure drops and the ventilator can sense the inspiratory effort. Clinically this is seen when the patient makes a visible effort and there is a delay in ventilator recognition (delayed trigger) or, if severe enough, no recognition at all (missed trigger). Esophageal manometry, which tracks changes of pleural pressure, is helpful in identifying patient work of triggering and the amount of auto-PEEP that is present. Figure 1 demonstrates a significant delay from the patient’s initiation of a breath (esophageal tracing) to the ventilator’s recognition of an effort (flow and Vt tracings). This delay is due to the need for the patient to first overcome the auto-PEEP. It is important to bear in mind, however, that esophageal manometry requires special equipment and placement skills. When auto-PEEP is the cause, solutions to avoiding delayed and missed triggering include careful reassessment of the ventilator settings, (particularly to see whether the inspiratory time can be shortened). Bronchodilation can be used to ease the obstruction, or applied PEEP can be used to minimize the triggering pressure gradient between the patient and the ventilator.

Figure 1. The esophageal tracing illustrates the delay from the patient’s initiation of a breath to the ventilator’s recognition of an effort.

The prudent use of applied PEEP can be helpful when there is flow limitation during
tidal exhalation. The aim of applied PEEP in this case is not to improve oxygenation but rather to decrease the pressure gradient between the alveolar and circuit pressures. Narrowing that pressure difference reduces patient effort to trigger. **Figure 2** illustrates the tendency for delayed and missed triggers (negative deflections on the esophageal pressure tracing in top frame) to be offset by the addition of external PEEP (esophageal tracing in bottom frame). Note that the size of the negative deflection in the esophageal tracing is less in the bottom frame, indicating a decrease in work of triggering. Clinically, the clinician sees the patient not exerting as much work to trigger and fewer missed triggers. However, caution must be exercised when pressure-targeted modes are used, because PEEP increases may increase the effectiveness of the applied inspiratory pressure and therefore the Vt.

**Figure 2. Tendency for delayed and missed triggers**

![Figure 2. Tendency for delayed and missed triggers](image)

Top frame: Positive end-expiratory pressure level 0 cm H₂O, multiple missed breaths. Bottom frame: 15 cm H₂O added, decrease in the number of missed breaths.

Auto-triggering is another form of trigger asynchrony that occurs when the ventilator misperceives a circuit pressure drop or flow change as an effort from the patient. It can be caused by an overly-responsive sensitivity setting on the ventilator, system leaks, or large oscillations of airway pressure resulting from hyperdynamic cardiac activity. In adults, system leaks can result from a loose connection in the circuit or a tube cuff leak. Although not used as often today, uncuffed endotracheal tubes in neonates also can result in system leaks that lead to auto-triggering.

The poorly understood “reverse triggering” phenomenon involves a unique type of neuromechanical asynchrony where deeply sedated patients initiate a breath during an ongoing breath that seems to occur in heavily sedated patients. It is usually observed near the end of a ventilator-delivered breath; and can occur in a fixed ratio. This is illustrated in **Figure 3** where reverse triggering occurs in 1:1 (top panel), 1:2 (middle panel) and 1:3 (bottom panel) ratios. In theory, repeated “plyometric contractions” of the diaphragm caused by reverse triggering potentially could lead to the release of proinflammatory mediators and perhaps even to direct damage to the muscle fibers of the diaphragm. Strategies for attempting to stop reverse triggering include lightening sedation (if the patient tolerates it) or, conversely, initiating deeper
sedation or paralysis. It must be emphasized that no adverse consequence of this recently described phenomenon has been documented.

**Figure 3.** Reverse triggering

![flow asynchrony diagram]

I) 1:1 ratio, II) 2:1 ratio, III) 3:1 ratio.

**FLOW ASYNCHRONY**

Flow asynchrony occurs when ventilator flow delivery pattern does not match the inspiratory pattern of the patient’s muscular effort. Ventilator flow may be too fast, too slow, or improperly contoured. Flow asynchrony can occur during both VACV and PACV. In VACV, the clinician sets the flow and flow profile that will be delivered. In PACV, the clinician sets/adjusts the rise time (also referred to as slope or “attack” rate), which determines how quickly the set pressure target is reached.

In VACV, if the flow is too rapid, which tends to happen when minute ventilation demand is low, the breath will end prematurely. The result is that a single patient effort can initiate two consecutive breaths, often referred to as “double triggering.” On the other hand, if the patient’s inspiratory demand is higher than the ventilator’s set-delivered flow, patient WOB increases in an attempt to draw more rapid flow. The patient ends up generating negative intrathoracic pressures, as indicated by a downward deflection of the pressure waveform while the flow and volume waveforms remain constant (**Figure 4**). This is sometimes referred to as “flow starvation” and is more common in VACV because flow delivery magnitude and pattern are fixed and not variable.

**Figure 4.** Flow starvation
The patient is trying to get more flow from the ventilator but, since the tidal volume and flow are fixed in volume assist-control ventilation, the only waveform that is affected is the pressure waveform. The patient is pulling against the ventilator and the result is a downward deflection of pressure.

If flow starvation is present, the clinician has some options. The peak flow setting on the ventilator can be adjusted until the starvation disappears, keeping in mind that patient flow demand may be variable and no one adjustment may solve it. Modification of the flow delivery waveform (e.g., switching from decelerating to rectangular [square] pattern) may also prove helpful. However, turning up the flow rate shortens the inspiratory time, which now may be shorter than tolerated. Another option is to switch to a pressure-targeted mode to take advantage of a variable flow delivery that is more responsive to the patient’s needs. The drawback to this option is that the VT is no longer regulated or guaranteed. On the other hand, to correct flow asynchrony due to excessive ventilator flow, the clinician should turn down the flow while observing the patient until the ventilator’s and patient’s inspiratory times are more closely matched (this will result in a longer inspiration time so it is important to monitor for cycling asynchrony).

Flow asynchrony may also occur when the patient encroaches on the upper limits of the chosen settings (i.e., neonatal mode versus pediatric or pediatric versus adult). For instance, neonatal settings may be insufficient for the infant with a large inspiratory demand; changing to pediatric mode will increase the maximum inspiratory flow. Also, in neonates and very young children, PACV with an inspiratory flow dictated by the ventilator rather than by the clinician may cause an overshoot because the rise time is too quick. Switching to a mode in which the clinician can set the inspiratory flow seems preferable if simply adjusting rise time proves ineffective.

**CYCLING ASYNCHRONY**

Cycling asynchrony refers to a discrepancy between the termination of patient inspiratory effort and ventilator breath termination. This problem can come in the form of either premature or delayed cycling. Premature cycling occurs when the patient’s inspiratory effort continues after the ventilator cycles to exhalation.
Graphically this can be seen on the flow tracing as flow reversals after the ventilator has terminated the breath or, if severe enough, as a double breath (Figure 5). In VACV, premature cycling can be corrected by slowing the set inspiratory flow or by increasing the Vt. In PACV, this can be overcome by prolonging the inspiratory time. In PSV, the expiratory sensitivity can be adjusted to lengthen or shorten the inspiratory time as needed.

*Figure 5.* A single patient effort results in two breaths from the ventilator.

Delayed cycling occurs when the patient’s neural inspiratory time is shorter than the ventilator’s set inspiratory time (Figure 6). Graphically, a spike in the pressure waveform is seen as the patient tries to exhale against a closed exhalation valve (Figure 7). In VACV, this can be corrected by turning the flow rate up or the Vt down. In PACV, the inspiratory time can be directly adjusted to match the patient’s exhalation timing. Another option is to switch to PSV and use the expiratory sensitivity to find a better match for exhalation timing. Temporarily doing so may help the clinician gauge and then match the desired neural inspiratory time after return to pressure or volume control mode. Some ventilators have the ability to enable flow cycling on mandatory breaths in PACV. Usually, by default most ventilators set the flow cycling criteria at 25% for adults and 15% for pediatric patients. This means that, for adults, at least 75% and, for children, 85% of the inspiratory flow must be delivered before the ventilator cycles off to exhalation. Titrating flow cycling often is not easy and requires careful observation of the patient while adjusting the ventilator.

*Figure 6.* Delayed cycling.
Breath A represents the ventilator and patient in sync when cycling to exhalation. Breath B represents the patient’s neural inspiratory time being shorter than the ventilator’s delivered inspiratory time, resulting in an excessively long inspiratory time.


**Figure 7.** Delayed cycling

The patient attempts to exhale against a closed exhalation valve. This leads to an increase in pressure as can be seen in the pressure-time waveform (circles).

**MODE ASYNCHRONY**

Occurring mainly in SIMV, mode asynchrony is a pattern in which the ventilator delivers a combination of volume-targeted and pressure-supported breaths. Unfortunately, at any given level of machine support, the force generated by the patient is similar for both spontaneous and mandatory breaths. Consequently, because the patient is unsure which type of breath will be received, he/she may be confused by the response from the ventilator. In theory this might lead to a lack of adaptation by the patient, resulting in ineffective unloading of the respiratory muscles. The clinical consequences of this type of asynchrony are uncertain and may be under-recognized at the bedside. Nonetheless, clinicians should realize that it may occur when this mode is used.

SIMV has been shown to produce higher rates of PVA than PSV, VACV, or PACV, but it is still used today, probably because of tradition and familiarity. Also, relatively healthy patients without cardiothoracic or neurologic comorbidities can tolerate SIMV (as well as the other modes) for brief periods because they generally require little
ventilatory support. To summarize, PVA can occur in three specific phases of the ventilator-delivered breath or can result from mixing modes of breath delivery (SIMV). Depending on the cause of PVA, solutions usually involve adjustment of one or more ventilatory settings. Table 1 outlines the different types of PVA and some possible solutions.

<table>
<thead>
<tr>
<th>Type of PVA</th>
<th>Cause</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trigger</strong></td>
<td>Ineffective trigger:</td>
<td>Assess respiratory drive</td>
</tr>
<tr>
<td></td>
<td>Low respiratory drive</td>
<td>Reset sensitivity</td>
</tr>
<tr>
<td></td>
<td>Incorrect sensitivity setting</td>
<td>Increase set PEEP level</td>
</tr>
<tr>
<td></td>
<td>Dynamic hyperinflation (auto-PEEP)</td>
<td>PACV: Increase Ti</td>
</tr>
<tr>
<td></td>
<td>Double trigger:</td>
<td>VACV: Decrease flow/increase Vt</td>
</tr>
<tr>
<td></td>
<td>Patient effort longer than ventilator inspiratory time</td>
<td>Suction</td>
</tr>
<tr>
<td></td>
<td>Coughing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Auto-trigger:</td>
<td>Check for circuit/cuff leak and/or adjust sensitivity</td>
</tr>
<tr>
<td></td>
<td>Ventilator delivers an assisted breath in the absence of patient effort</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reverse trigger:</td>
<td>Lighten sedation?</td>
</tr>
<tr>
<td></td>
<td>Neuromechanical uncoupling?</td>
<td></td>
</tr>
<tr>
<td><strong>Flow</strong></td>
<td>Ventilator flow patient demand:</td>
<td>VACV: Reduce flow setting.</td>
</tr>
<tr>
<td></td>
<td>Patient overwhelmed</td>
<td>PACV/PSV: Decrease inspiratory pressure setting.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PACV/PSV: Reduce rise time setting.</td>
</tr>
<tr>
<td></td>
<td>Ventilator flow patient demand:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flow starvation. Patient pulls against ventilator.</td>
<td>VACV: Increase flow setting (Ti will decrease) and/or change flow profile.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PACV/PSV: Increase inspiratory pressure.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PACV/PSV: Increase rise time setting.</td>
</tr>
<tr>
<td><strong>Cycle</strong></td>
<td>Premature termination</td>
<td>Increase inspiratory pressure (watch Vt).</td>
</tr>
<tr>
<td></td>
<td>Low PSV level</td>
<td>Decrease expiratory sensitivity (lower %).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase Vt or decrease flow.</td>
</tr>
<tr>
<td></td>
<td>In VACV, Vt/flow produce short Ti’s.</td>
<td>Increase set Ti.</td>
</tr>
<tr>
<td></td>
<td>PACV</td>
<td>VACV: Increase flow and/or decrease Vt.</td>
</tr>
<tr>
<td></td>
<td>Delayed termination</td>
<td>PACV: Decrease Ti.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSV: Increase expiratory sensitivity (higher % setting).</td>
</tr>
<tr>
<td><strong>Mode</strong></td>
<td>Patient unsure which type of breath will be received.</td>
<td>Switch to PACV/VACV/PSV.</td>
</tr>
</tbody>
</table>

**TABLE 1. Types of Patient-ventilator Asynchronies and Potential Solutions**

Abbreviations: PACV, pressure assist-control ventilation; PEEP, positive end-expiratory pressure; PSV, pressure support ventilation; PVA, patient-ventilator asynchrony; Ti, inspiratory time; VACV, volume assist-control ventilation; Vt, tidal volume.

**IMPORTANCE OF RECOGNIZING PATIENT-VENTILATOR ASYNCHRONY**

PVA should not be overlooked. In adults, both the asynchrony index (the percentage of breaths by which the patient is out of sync with the ventilator) and the ineffective trigger index (the percentage of breaths not correctly followed by the ventilator) have been associated with increased sedation use, prolonged duration of MV, higher levels of PSV, and longer ICU and hospital stays in mechanically ventilated
adults. It remains to be determined whether this also holds true for children.

**HOW TO DETECT PATIENT-VENTILATOR ASYNCHRONY**

Classically, PVA can be detected by observing the respiratory efforts of the patient and the resulting ventilator waveforms—pressure-time, flow-time, pressure-volume, and flow-volume. Most ventilators display these waveforms and have the ability to freeze screens for careful examination. However, it may be questioned whether simply observing waveforms, especially in pediatrics, picks up all PVA. Monitoring the electrical activity of the diaphragm (EAdi), an option in patients receiving neurally adjusted ventilatory assist (NAVA), provides precise information on the patient’s neural activity; however, this requires the insertion of a special esophageal catheter, which may be cumbersome in small children.

At present, no specific criteria for detecting and correcting PVA have been published for pediatric patients. In adult critical care, it is commonly accepted that esophageal manometry combined with respiratory muscle electromyography (EMG) and simultaneous evaluation of the flow, pressure, and volume signals may provide the most accurate assessment of patient-ventilator interactions. The former two methods, however, are seldom used in day-to-day practice.

**ARE ALL-AROUND VENTILATORS SUITABLE FOR YOUNG CHILDREN?**

Ventilator characteristics themselves may contribute to PVA. Nowadays, versatile ventilators are used in the ICU; it is claimed that they are able to ventilate the entire range of patients, from neonates to adults. But infants have a much higher breathing drive than adults. In addition, uncuffed endotracheal tubes are more often used in infants and small children, but this practice inevitably results in some degree of leakage. Leakage can result in patient-initiated flow changes below the detection threshold. Conflicting results have been reported. While in one bench model of commonly used ICU ventilators, the trigger sensitivity was not affected by the presence of air leakage, other studies have reported otherwise. So it cannot be ruled out that ventilators may fail to identify an inspiratory effort in small children in the presence of endotracheal tube leakage.

**NEW MODES SPECIFICALLY DESIGNED TO OPTIMIZE PATIENT-VENTILATOR INTERACTIONS**

Recently two new modes of ventilation have become available that are designed to optimize patient-ventilator interactions. They are proportional assist ventilation (PAV) and neurally adjusted ventilatory assist (NAVA). Both modes respond almost instantaneously to the patient’s inspiratory demand and attempt to reduce patient effort to a preset degree. In essence they amplify the patient’s effort, using the ventilator to mimic an auxiliary set of muscles, thereby reducing the WOB to a level set by the clinician.

Although often viewed as a new mode of ventilation, the concept of PAV was first described in 1992. PAV amplifies the patient’s own inspiratory effort by increasing or decreasing airway pressure and flow in conjunction with patient effort. Unlike pressure-regulated volume control, the pressure applied by the ventilator varies during the breath rather than being based on previous breaths (PAV also does not target a set Vt). Figure 8 graphically illustrates PAV. Note that all three tracings
(pressure, flow, and Vt) vary in accordance with patient effort. The software algorithm underlying the technology continuously and automatically adjusts the pressure and flow based on patient demand throughout the inspiratory cycle to maintain the set degree of support. The ventilator frequently samples the compliance and resistance, and the algorithm driving PAV then converts this information, together with measures of expired flow and volume, into an estimate of the total WOB. The machine can provide a set fraction of that requirement, according to the value set by the clinician. It is displayed as a WOB bar (Figure 9). The clinician directly sets the WOB (the amount of work that the ventilator will contribute). For instance, if 60% WOB is set on the ventilator, then 60% of the WOB during every breath will be provided. In this example, the patient is required to assume the other 40%. An increased inspiratory effort by the patient (increasing the total WOB for the breath) results in increased support from the ventilator to keep its contribution to the breath at 60% of the total. The reverse, however, is also true. If the patient generates smaller inspiratory efforts, the support from the ventilator will decrease (but will still be at 60% of the total WOB for that particular breath).

**Figure 8.** Proportional assist ventilation

Note that the pressure, flow, and tidal volume tracings all vary in accordance with patient effort.

**Figure 9.** Proportional assist ventilation
Work of breathing screen.

This differs from PSV, in which changes in inspiratory effort are met with the same pressure throughout the breath. Triggering of the breath to inspiration in PAV is accomplished in the same manner as conventional ventilation. Cycling to exhalation in PAV occurs when the flow diminishes to the set threshold (e.g., when flow reaches 3 liters per minute) as opposed to a flow decay percentage threshold, as is the case in PSV. Although PAV allows backup settings, it is important to bear in mind that patients must have a reliable respiratory drive for the mode to function as intended.

A number of studies have examined patient-ventilator synchrony, comparing PAV with PSV. End points usually were the number of observed asynchronies. Most of the studies were relatively small but in general they favored PAV as being more synchronous than PSV, especially at levels of high minute ventilation. Unfortunately no meaningful outcome studies have been performed to date, so we cannot assume that improved patient-ventilator synchrony decreases weaning time (and duration of MV) or that it improves mortality rate. The main barriers to the use of PAV are lack of clinician familiarity and limited availability, (most ventilators don’t offer PAV) on only very few brands of ventilator. Clinicians must now think in terms of WOB instead of setting a specific pressure level. As well, many institutions do not have access to ventilators adapted for PAV software.

NAVA accomplishes the same goal as PAV but, instead of expired flow and mechanics measurements, relies on the diaphragmatic EMG signal to detect patient triggers and guide inspiratory gas delivery. A specifically designed nasogastric tube equipped with a series of EMG electrodes near its distal end captures the EMG activity of the diaphragm and passes the information back to the ventilator, which maintains respiratory support (pressure and flow) proportional to the signal strength. As the ventilator and the diaphragm work with the same signal, mechanical coupling between the diaphragm and the ventilator is practically instantaneous. As EMG activity increases, the applied pressure increases and, conversely, airway pressure
decreases as the diaphragm relaxes. The clinician sets the pressure applied for each microvolt of EMG activity and, as with PAV, the effort is proportionally distributed between the ventilator and the patient. The level of support from one cycle to the next is directly proportional to the EMG activity.

In theory, NAVA optimizes patient-ventilator interaction in all three phases of the inspired delivered breath. The trigger signal is based on a set level of EAdi, measured in microvolts. Once triggered, the breath is delivered based on a certain level of pressure (set by the clinician) per microvolt. The breath ends when the EAdi reaches a preset decay level. Figure 10 illustrates the waveforms in NAVA. The first three waveforms are the typical pressure, flow, and volume tracings. There is now a fourth waveform, which is the EAdi tracing. Note that the pressure, flow, and volume tracings are mirror images of the EAdi tracing.

*Figure 10.* Neurally adjusted ventilatory assist

Like PAV, there have been a number of studies comparing NAVA to PSV in terms of patient-ventilator interactions. It appears that NAVA may offer potential interaction advantage. As for noninvasive ventilation, several studies show that NAVA reduces the inspiratory trigger delay, harmonizes the patient’s switch to expiration with the cycling off of the machine, and reduces asynchronies between the patient and the ventilator. Evidence in the neonatal arena has shown similar outcomes as in the adult studies regarding improved synchrony. At least one study
reported no differences in triggering and cycling synchrony during invasive as compared to noninvasive ventilation using NAVA control.\textsuperscript{25}

Evidence indicates that both PAV and NAVA may improve neuromechanical coupling and improve patient-ventilator synchrony compared with conventional modes of ventilation. They also help patients establish a ventilatory pattern more consistent with their inspiratory demands. Unfortunately there are currently no good randomized trials looking at outcome benefits such as mortality and ventilator duration when using these novel modes.

CONCLUSION

PVA is a real phenomenon that occurs when the patient is out of sync with the ventilator. It can occur at the beginning of a ventilator-delivered breath, during flow delivery, and at the end of a breath. It can also occur during a mixed-mode type of ventilation (SIMV) when the patient is uncertain which type of breath will come next. Solutions to PVA involve careful assessment in matching the patient to the graphics and then making appropriate parameter adjustments. Reducing minute ventilation demand minimizes intolerance of the neural controller and therefore helps dramatically to restore patient-ventilator synchrony. PAV and NAVA are two new modes of ventilation designed to optimize patient-ventilator synchrony. However, more study needs to be done before they will see mainstream use in the clinical arena.

KEY POINTS

- Patient-ventilator asynchrony (PVA) can occur upon breath initiation, during delivery, and at the termination of a breath.
- PVA occurs more commonly in patients with higher ventilatory demands.
- Trigger asynchrony occurs when the ventilator does not appropriately detect patient efforts or delivers a breath in the absence of patient effort.
- Flow asynchrony occurs when there is a mismatch between the patient’s flow demand and the flow that the ventilator delivers during the breath.
- Cycling asynchrony occurs when the ventilator breath termination and the patient’s neural breath termination do not line up.
- Solutions for PVA involve appropriate graphical waveform analysis and subsequent ventilator parameter adjustment.
- PAV and NAVA are two newer modes of ventilation specifically designed to optimize patient-ventilator synchrony.

REFERENCES

4. Chao DC, Scheinhorn DJ, Stearn-Hassenpflug M. Patient-ventilator asynchrony in prolonged
Patients with asthma and chronic obstructive pulmonary disease (COPD) may require mechanical ventilation for respiratory failure related to acute exacerbations of underlying airway disease or due to an intercurrent critical illness. Regardless of the indication for mechanical ventilation, it is important that the intensivist understand certain key principles related to ventilator management of patients with severe airflow obstruction in order to lessen the risk of complications.1–5

RESPIRATORY MECHANICS

Patients with severe airflow obstruction invariably have increased inspiratory and expiratory airway resistances. The latter reduces expiratory gas flow, predisposing to pulmonary hyperinflation. During volume-cycled ventilation, increased inspiratory resistive pressure and hyperinflation together lead to an increase in peak airway pressure (Ppk). Introduction of an end-inspiratory pause permits measurement of the end-inspiratory plateau pressure (Pplat), while auto-positive end-expiratory pressure (auto-PEEP) is assessed with an end-expiratory pause (Figure 1). Under passive conditions, the amount of dynamic hyperinflation can be estimated by the level of auto-PEEP, which is the amount of end-expiratory static pressure in excess of applied PEEP. Since Pplat is measured under no-flow conditions, it is not directly affected by inspiratory airway resistance; in patients with airflow obstruction ventilated with a constant tidal volume, it also provides an estimate of the degree of hyperinflation.

Figure 1. Schematic representation of airway pressure (top) and flow (bottom) during controlled mechanical ventilation
Note that flow persists at end-expiration, indicating that end-expiratory alveolar pressure must exceed circuit pressure (i.e., auto-PEEP is present). Note that during the end-inspiratory airway occlusion, there is an initial rapid fall from peak airway pressure ($P_{Ppk}$) to $P_1$, due to dissipation of pressure related to intrinsic airway resistance, followed by a more gradual fall to $P_2$ (plateau pressure [$P_{PLAT}$]) due to gas redistribution and stress relaxation. The dotted line represents alveolar pressure ($P_{ALV}$).

The difference between $P_{Ppk}$ and $P_{PLAT}$ (flow-resistive pressure) is often greatly increased in patients with airflow obstruction. This occurs primarily as the result of an increase in intrinsic airway resistance, but a second cause relates to inhomogeneity within different lung units. During a prolonged end-inspiratory airway occlusion, the sudden interruption in flow causes the pressure to drop rapidly from $P_{Ppk}$ to an initial pressure at the point of flow cessation, and then more gradually to a final pressure that is recorded as $P_{PLAT}$ (Figure 1). The initial fall in pressure is a reflection of intrinsic airway resistance. The subsequent fall from initial pressure to final pressure is caused by gas redistribution within the lung (pendelluft) and dissipation of pressure related to viscoelastic properties of the pulmonary parenchyma and chest wall (stress relaxation). Unlike healthy people (or patients with ARDS), patients with severe airflow obstruction may require an inspiratory pause of several seconds' duration for a plateau in pressure to be reached. This is because the lung in asthma and COPD is characterized by considerable inhomogeneity in local airway resistances, resulting in regional differences in filling and emptying of alveoli and significant gas redistribution within the lung during the end-inspiratory pause.

To assess the severity of airflow obstruction and the risk of complications, some authors have advocated limiting $P_{Ppk}$ (during flow) to less than 50 cm H$_2$O. Ppk is
greatly influenced by inspiratory airway resistance and by the choice of inspiratory flow rate and inspiratory waveform, but may not reliably reflect the degree of pulmonary hyperinflation, the most important risk factor for barotrauma and hypotension. For example, the large resistive pressure gradient generated when patients are managed with a high inspiratory flow rate (eg, 100 L/min) and a square inspiratory waveform often results in a Ppk that exceeds 50 cm H$_2$O, but this does not necessarily predict an increased risk of complications. For this reason, most authors have advocated a ventilator strategy that focuses on Pplat rather than Ppk. Notwithstanding the potential dissociation between Ppk and overall pulmonary hyperinflation, some authors still believe that limiting Ppk has a physiologic rationale. Their argument is that, while Pplat may represent the average end-inspiratory alveolar pressure, local alveolar pressure in the most vulnerable lung units will be higher, but can never exceed Ppk.

In the relaxed mechanically ventilated patient, three factors determine Pplat: tidal volume, respiratory system compliance, and end-expiratory alveolar pressure. Non-obese patients with obstructive lung disease typically have normal respiratory system compliance. As such, when they are ventilated with conventional tidal volumes, increases in Pplat are primarily the result of increased end-expiratory alveolar pressure. Although several authors have advocated using Pplat as the primary parameter to monitor in patients with severe airflow obstruction, robust evidence for this approach is lacking. Nonetheless, anecdotal evidence has suggested that asthmatic patients whose Pplat remains less than 30 cm H$_2$O have a very low incidence of serious complications. Most studies of mechanically ventilated patients with severe airflow obstruction have reported average Pplat values in the low to mid-20s. Auto-PEEP is invariably present in mechanically ventilated patients with airflow obstruction. Surprisingly, there has been relatively little published data on typical auto-PEEP values in patients with exacerbations of asthma or COPD. Values are often in the range of 10 to 15 cm H$_2$O (but may be higher). Auto-PEEP values in this range represent a significant degree of hyperinflation, but are usually well tolerated. To assess hyperinflation, auto-PEEP should be measured by the static method, using an end-expiratory occlusion, during which airway pressure may continue to rise for several seconds. Premature termination of expiratory airway occlusions, as may occur with the ventilator's automated program, can lead to significant underestimation of average end-expiratory alveolar pressure. On occasion, patients with fulminant asthma who are ventilated at very low respiratory rates may have low values of measured auto-PEEP, presumably as a result of airway closure that eliminates the communication between the external circuit and the sealed alveolar compartment, preventing accurate assessment of true end-expiratory alveolar pressure. When measuring auto-PEEP, it is critical that the patient be completely relaxed. Activation of expiratory muscles during the airway occlusion may cause the measured value to greatly overestimate the degree of hyperinflation. Expiratory muscle activity is not always evident by bedside examination, especially in obese patients. When auto-PEEP remains markedly elevated despite sedation, repeat assessment after a brief period of neuromuscular paralysis is recommended.

PULMONARY HYPERINFLATION: INFLUENCE OF VENTILATOR SETTINGS

Pulmonary hyperinflation is a hallmark of the mechanically ventilated patient with
severe airflow obstruction. During controlled mechanical ventilation of patients without airflow obstruction, there is normally sufficient time during exhalation for the lung to return to its relaxed volume (functional residual capacity) (Figure 2). In contrast, patients with airflow obstruction have incomplete exhalation of delivered tidal volume with an increase in end-expiratory lung volume above functional residual capacity (Figure 2). With subsequent tidal breaths, the progressive increase in lung volume is accompanied by larger airway diameter and higher elastic recoil pressure, leading to greater expiratory flow. As such, a steady state is quickly reached, and delivered tidal volume is completely exhaled, but at the cost of a higher end-expiratory lung volume and alveolar pressure (Figure 2).

Figure 2. Airway obstruction

A, Dynamic hyperinflation. B, Measurement of $V_{EE}$ and $V_{DH}$ by use of a prolonged apnea beginning at end-inspiration. $V_{EE}$ and $V_{DH}$ are equivalent.

Abbreviations: FRC, functional residual capacity; $T_e$, expiratory time; $T_i$, inspiratory time; $V_{DH}$, volume (above FRC) due to dynamic hyperinflation; $V_{EE}$, volume (above FRC) at end-expiration; $V_{EI}$, volume (above FRC) at end-inspiration; $V_T$, tidal volume.


Minute Ventilation

One method of quantifying the degree of dynamic hyperinflation is to measure the volume of gas that can be exhaled during a prolonged apnea, beginning at the end of a tidal breath. The volume of gas exhaled is the sum of the delivered tidal volume and additional volume due to dynamic hyperinflation (Figure 2). Using this technique, Tuxen and colleagues assessed the impact of different ventilator settings during mechanical ventilation of patients with severe airflow obstruction. They found that the most important determinant of dynamic hyperinflation was minute
ventilation. For a given minute ventilation, the degree of hyperinflation was similar, with varying combinations of respiratory rate and tidal volume, but use of a higher tidal volume and lower respiratory rate would, of necessity, result in a higher end-inspiratory lung volume and maximal alveolar pressure than would a lower tidal volume/higher respiratory rate strategy. When patients with airflow obstruction were managed with very high minute ventilation (16 and 26 L/min), hyperinflation reached levels that greatly increased the risk of hemodynamic collapse and pneumothorax. Without question, the use of very high levels of minute ventilation in the setting of severe airflow obstruction can lead to marked hyperinflation with the potential for catastrophic consequences, including death. However, the benefit of extreme limitation of minute ventilation is less certain. For example, when asthmatic patients who were ventilated with a tidal volume of 600 mL underwent a reduction of their respiratory rate from 12 to 6 breaths/min (adding 5 seconds of expiratory time), the reduction in hyperinflation was relatively modest, as evidenced by only a 2–3 cm decrement in auto-PEEP and Pplat (Figure 3). The latter observation is readily explained by the relatively low expiratory flow rates that occur after a few seconds of exhalation (Figure 4). Furthermore, since expiratory gas flow progressively decreases over time, the benefit of a given prolongation of expiratory time on dynamic hyperinflation will be less at lower respiratory rates (Figure 4). In other words, when expiratory time is relatively brief due to a high respiratory rate (eg, greater than 20 breaths/min), prolonging expiratory time by reducing the respiratory rate can have a major impact on the degree of hyperinflation. In contrast, when expiratory time is already several seconds in duration, further prolongation of expiratory time will have only a modest impact on lung volume. In addition, a certain amount of the overall pulmonary hyperinflation in asthma may be due to gas trapped behind occluded airways that is not amenable to manipulation of machine settings. In brief, with a tidal volume of approximately 8 mL/kg ideal body weight, there is usually little to be gained by reducing the respiratory rate below 10–14 breaths/min. One exception might be when hyperinflation has resulted in complications such as barotrauma or hypotension, because even a small reduction in lung volume could have a meaningful clinical impact.

Figure 3. Plateau pressure and auto-PEEP during mechanical ventilation for severe asthma measured at respiratory rates of 18, 12, and 6 breaths/min (tidal volume approximately 600 mL).
Inspiratory Flow Rate and Inspiratory Waveform

Inspiratory flow rate and inspiratory waveform also influence expiratory time. For a given minute ventilation, use of a higher inspiratory flow rate will provide more time for exhalation. Similarly, a square inspiratory waveform will yield a shorter inspiratory time and longer expiratory time than will a decelerating waveform. For this reason, it has been suggested that a high inspiratory flow rate (eg, 100 L/min) and a square
inspiratory waveform be used for patients with severe airflow obstruction. Such high flow rates boost Ppk and, at least in theory, may carry risks of their own. Moreover, such a strategy typically results in only minor prolongation of expiratory time (Table 1). Given the low end-expiratory flow rates when minute ventilation has already been limited, this modest extension of expiratory time is unlikely to provide a clinically meaningful reduction in lung volume. In the original studies by Tuxen and colleagues, inspiratory flow rate was a major determinant of dynamic hyperinflation at high levels of minute ventilation (16 and 26 L/min), but had negligible impact when minute ventilation was 10 L/min. In brief, inspiratory flow rate and waveform have minimal impact on the degree of hyperinflation once minute ventilation has been limited.

Most modern ventilators display the inspiratory-to-expiratory (I:E) ratio on a breath-by-breath basis; it is intuitive that patients with airflow obstruction may benefit by having a low I:E ratio. However, it is misleading to focus excessively on the I:E ratio. As already noted, use of a very high flow rate can produce a favorable I:E ratio yet have minimal effect on expiratory time (Table 1). In addition, patients who are not deeply sedated or who are paralyzed may respond to a shortening of inspiratory time by increasing respiratory frequency, thereby offsetting any potential benefit with regard to extension of expiratory time.

Although use of a very high flow rate and a square waveform may offer little benefit to the patient with airflow obstruction, it is not clear that this strategy would be harmful. As noted earlier, use of high flow rates and a square waveform in the setting of increased airway resistance often results in a marked increase in Ppk, but whether this exposes the patient to increased risk of complications is doubtful. Nonetheless, since more conventional flow rates (eg, 60–70 L/min) and a decelerating waveform will yield a much lower Ppk without a clinically meaningful increase in the degree of hyperinflation, the latter approach is recommended.

**Applied Positive End-Expiratory Pressure**

The effect of external PEEP on respiratory mechanics has been extensively studied in patients with COPD, who typically have classic expiratory flow limitation, in that expiratory flow is governed by the resistance in flow-limiting segments of the small airways, rather than by the difference between alveolar pressure and external PEEP. Application of external PEEP up to approximately 80% of auto-PEEP has negligible effect on expiratory flow, lung volume, or cardiac output (Figure 5a). The analogy that has been used to explain this phenomenon is a waterfall, in that downstream pressure (external PEEP) does not influence flow over the waterfall or upstream pressure (auto-PEEP) until it nearly exceeds the latter (Figure 5b).
brief, during controlled mechanical ventilation of tidally flow-limited patients with COPD, adding external PEEP at levels up to approximately 80% of auto-PEEP may in theory help improve the evenness of ventilation by reducing differences in regional auto-PEEP, but typically appears neutral in that it has neither harmful nor markedly beneficial clinical effects.

**Figure 5.** A: Change in end-expiratory lung volume (EELV) as a function of the ratio of applied PEEP to auto-PEEP, with the latter measured in the absence of PEEP. B: The waterfall concept to explain expiratory flow limitation.

This ratio is expressed as applied PEEP/PEEPtot, rs on ZEEP. Note that EELV does not change when applied PEEP is less than or equal to 80% of auto-PEEP. The downstream airway pressure (Paw) is applied PEEP; the upstream end-expiratory alveolar pressure (Palv) is intrinsic PEEP (PEEPi), another term for auto-PEEP. As long as applied PEEP remains below a critical pressure (Pcrit), typically about 80% of auto-PEEP, it will not influence end-expiratory Palv.

Abbrivation: ZEEP, zero end-expiratory pressure.


In contrast, when patients with COPD are attempting to trigger the ventilator or draw a spontaneous breath, external PEEP is often beneficial because it reduces the inspiratory effort required to initiate a breath ([Figure 6](#)). For example, consider a patient with COPD with an auto-PEEP of 14 cm H₂O whose trigger sensitivity is set at 2 cm H₂O below the level of applied PEEP. If there is no external PEEP, it will require an inspiratory effort of –16 cm H₂O to activate the ventilator. This is equivalent to setting the trigger sensitivity at a highly negative value in a patient without auto-PEEP. Besides having to generate more negative pressure to trigger the ventilator, high levels of auto-PEEP signal the presence of significant hyperinflation that places the inspiratory muscles at a disadvantage due to diaphragm flattening and the need to overcome greater inward elastic recoil of the chest wall. Together, these factors can impede the patient from initiating inspiration ([Figure 7](#)). Being essentially “locked out” of interacting with the ventilator can lead to significant patient-ventilator dyssynchrony and can be very distressing for the patient. On the other hand, if the same patient, with an auto-PEEP of 14 cm H₂O is placed on an applied PEEP of 10 cm H₂O (trigger threshold at a circuit pressure of 8 cm H₂O), it will now require an effort of only –6 cm H₂O, a significant reduction in the amount of inspiratory effort required to trigger the ventilator. Therefore, in patients with...
COPD who are actively triggering the ventilator, use of external PEEP at values up to 80% of auto-PEEP can significantly decrease the work of breathing and greatly improve patient comfort.

**Figure 6.** Impact of applied PEEP on the inspiratory effort required to trigger the ventilator

In the presence of auto-PEEP, the inspiratory pressure (measured as esophageal pressure, Pes) that must be generated to trigger the ventilator is less when PEEP is applied.

Abbreviation: Palv, alveolar pressure.


**Figure 7.** Schematic representation of flow, airway pressure ($P_{aw}$) and esophageal pressure ($P_{es}$) in a patient breathing in the pressure support mode
Inspiratory efforts that do not trigger the ventilator are indicated by arrows.


Unlike COPD, the effect of external PEEP in asthma has not been well studied. It has been suggested that the nature of the airflow obstruction in COPD and asthma might be fundamentally different and that the response to external PEEP may be different in these two disorders (Figure 8). In the single published study that focused specifically on mechanically ventilated asthmatic patients, both lung volume and Pplat were increased by 10–15 cm H$_2$O of external PEEP.$^{14}$ One of the limitations of this study was that auto-PEEP was not measured before application of external PEEP. Therefore, it is not certain if the increase in lung volume was simply due to the use of external PEEP that exceeded auto-PEEP.

**Figure 8.** The effect of applied PEEP on airway pressure (Paw) in two hypothetical patients with auto-PEEP.
Top: No change in airway pressure until applied PEEP exceeds auto-PEEP indicative of expiratory flow limitation as typically seen in COPD. Bottom: Airway pressure increases at applied PEEP levels below auto-PEEP, a pattern seen in some patients with asthma.


A more recent prospective study examined the effect of PEEP on lung volume and airway pressures in patients with asthma and COPD who were ventilated with different combinations of tidal volume and respiratory rate. The authors observed three distinct responses to applied PEEP: 1) a neutral response, with PEEP having no effect on lung volume or Pplat until it approximated auto-PEEP (classic expiratory flow limitation), 2) a detrimental response, with an increase in both lung volume and Pplat even at levels of applied PEEP well below auto-PEEP, and 3) a beneficial response, with a reduction in both lung volume and Pplat in response to PEEP (paradoxical deflation) (Figure 9). The type of response was not predicted by the underlying cause of airflow obstruction (ie, COPD vs. asthma). Furthermore, different patterns of PEEP response were observed in the same patient at different ventilator settings.

Figure 9. Effect of a stepwise increase in external PEEP (as a percentage of auto-PEEP) on lung volume, plateau pressure (P_{PLAT}), and total PEEP (defined as the measured end-expiratory occlusion pressure) in patients with airflow obstruction
Three types of response are depicted: A) classical expiratory flow limitation (no change in lung volume, \(P_{\text{plat}}\), or total PEEP until external PEEP exceeds auto-PEEP); B) Overinflation (increased lung volume, \(P_{\text{plat}}\), and total PEEP at levels of applied PEEP below auto-PEEP); and C) “paradoxical deflation” (decrease in lung volume, \(P_{\text{plat}}\), and total PEEP).


Given the conflicting data regarding the effects of PEEP in ventilated patients with airflow obstruction, what is the most rational approach to using it at the present time? In the author’s opinion, PEEP is unlikely to have a major beneficial effect on lung volumes or airway pressures during controlled mechanical ventilation of patients with either COPD or asthma, so that use of minimal levels of PEEP (0–5 cm H\(_2\)O) is recommended. If a trial of incremental PEEP is undertaken to search for the rare patient who might demonstrate a paradoxical deflation response, the trial should be terminated immediately if \(P_{\text{plat}}\) increases. The recommendation to use low-level PEEP is limited to patients undergoing controlled mechanical ventilation. Once the patient’s sedation is lightened and the patient is encouraged to actively trigger the ventilator, the use of PEEP up to 80% of auto-PEEP may have significant benefit by enhancing trigger sensitivity, thereby decreasing work of breathing and improving overall patient comfort.

Recently, significant levels of auto-PEEP were documented in morbidly obese patients (BMI >35) who did not have a prior history of airway disease. In one study, the average auto-PEEP was 10 cm H\(_2\)O in obese patients when supine, but was negligible when sitting up in bed. All such patients showed evidence of classic
expiratory flow limitation (similar to that in COPD) while supine, in that application of external PEEP up to the level of auto-PEEP had no effect on Pplat. This suggests the presence of small airway closure, perhaps due to the weight of the abdomen in morbidly obese patients who are ventilated while lying flat.

**HYPERCAPNIA**

In the absence of severe pneumonia or mucus plugging with atelectasis, hypoxemia during mechanical ventilation for exacerbations of COPD or asthma is generally responsive to modest increases in fraction of inspired oxygen $\text{Fi}_{O_2}$ (eg, ≤0.5). In contrast, at ventilator settings deemed to be safe with regard to limiting the degree of hyperinflation, hypercapnia is common. Although both asthma and COPD exacerbations are associated with hypercapnia, they differ in that patients with COPD typically have some degree of chronic hypercapnia with metabolic compensation while the hypercapnia in asthma is acute. As such, the degree of respiratory acidosis is generally much greater in asthma than in COPD. In acute severe asthma, initial partial arterial carbon dioxide pressure ($\text{Paco}_2$) values during the first few hours of mechanical ventilation are often greater than 70 mm Hg and may occasionally exceed 100 mm Hg, with a corresponding pH that is often less than 7.2. In the setting of fulminant asthma, the term “permissive” hypercapnia may not be entirely appropriate. Hypercapnia is a consequence of increased dead space ventilation caused by alveolar overdistention (as well as increased CO$_2$ production from metabolic stress). As such, increasing minute ventilation in an attempt to lower $\text{Paco}_2$ may worsen hyperinflation and lead to a further increase in physiologic dead space, mitigating the extent to which it will lower $\text{Paco}_2$.

Fortunately, serious adverse consequences from hypercapnia are uncommon in this setting, with cardiovascular and central nervous system effects being of greatest concern. Acute hypercapnia results in intracellular acidosis and a direct decrease in myocardial contractility, but sympathetic activation more than compensates for this effect, and cardiac output is typically increased (provided that beta-blockers were not in use). Increases of pulmonary vascular resistance due to acidosis, however, may stress the right ventricle in some patients. Arrhythmias are uncommon in the absence of underlying heart disease. Acute hypercapnia increases cerebral blood flow and intracranial pressure, an effect that would be of greatest concern when asthma-related cardiorespiratory arrest preceded intubation. Although hypercapnia-related cerebral edema and subarachnoid hemorrhage have been reported, they are fortunately rare.

Alkalizing agents are sometimes considered when arterial pH is persistently less than 7.15–7.20. Unfortunately, sodium bicarbonate is relatively inefficient as a treatment for respiratory acidosis. Even partial correction of severe respiratory acidosis may require several hundred milliequivalents of sodium bicarbonate. If bicarbonate is used, rapid boluses should be avoided since CO$_2$ that is produced in the process of buffering readily crosses cell membranes and can lead to a transient decrease in intracellular $\text{pH}$. If an alkalizing agent is deemed necessary, an alternative to sodium bicarbonate is tromethamine, which does not generate CO$_2$ or lead to a decrease in intracellular $\text{pH}$. It has been shown to partially reverse the myocardial depressant effect of acute hypercapnia. It should not be used in the presence of renal failure or hyperkalemia. Absent an urgent reason to correct
acidemia (e.g., serious arrhythmias, hyperkalemia, unexplained hemodynamic instability), it may be reasonable to withhold alkalinizing therapy and wait for hypercapnia to resolve with lessening of airflow obstruction. Many patients with acute asthma show improvement in hypercapnia during the first 12 hours of intubation.

In contrast to asthma, COPD exacerbations that lead to intubation are often characterized by acute-on-chronic respiratory acidosis. For patients with chronic hypercapnia, it is important to avoid normalizing Paco$_2$ during mechanical ventilation since the resultant alkalosis will stimulate renal bicarbonate excretion. As a result, the patient may develop significant acidosis when the Paco$_2$ returns to its baseline elevated level during a spontaneous breathing trial. Another acid-base problem that can arise occurs when patients develop an inappropriate degree of metabolic alkalosis, most often the result of diuresis. If excessive, this can cause a decrease in respiratory drive during attempts at weaning. If such a situation occurs, acetazolamide may help lower the serum bicarbonate, as long as overcorrection to a normal value is avoided.

**PHARMACOLOGIC THERAPY**

*Therapy of Airflow Obstruction: Bronchodilators and Corticosteroids*

Either a metered-dose inhaler or nebulizer can be used to administer bronchodilators. When delivery is optimal, the recommended dose of albuterol is four to six puffs by metered-dose inhaler or 2.5 mg by nebulization. Continuous nebulization of albuterol offers no clear advantage over intermittent therapy. It is important to recognize that use of very high doses of albuterol can lead to important side effects such as tachycardia, hypokalemia, and lactic acidosis. The latter is of particular concern in patients who already have respiratory acidosis. In patients with severe asthma, the combination of ipratropium and albuterol may provide a greater degree of bronchodilation than albuterol alone. Corticosteroids are an essential component of therapy for severe exacerbations of asthma and COPD. Optimal dosing of corticosteroids for patients who require mechanical ventilation for severe airflow obstruction has not been established, but 2 mg/kg/d of methylprednisolone or equivalent is likely adequate.

Steroids are essential for most intubated and ventilated patients with exacerbated airflow obstruction because they reduce inflammation, help inhibit generation of thickened mucus, and assist with clearance of existing airway mucus plugs. The latter problem may limit progress toward extubation, so that adequate hydration must be ensured and lubrication and lysis of preformed mucus may be aided by pharmacologic agents such as inhaled acetylcysteine (given with bronchodilator). Airway vibration may help in mobilizing retained secretions in patients with ineffective coughing, and multiple effective device options for accomplishing air column vibration are now available.

**Sedation and Paralysis**

In the presence of severe airflow obstruction, deep sedation is often initially needed to suppress respiratory drive and enforce controlled hypoventilation, and to achieve good patient-ventilator synchrony so that the patient is not fighting the ventilator. Either propofol or a benzodiazepine titrated to a moderate to deep level of sedation
will guarantee amnesia, while an opioid such as fentanyl provides analgesia, helps reduce the drive to breathe, and tends to alter the breathing pattern toward one of slower, deeper breaths. In some cases, severe airflow obstruction that initially necessitated deep sedation improves markedly within 24–48 hours. When high-dose benzodiazepine infusions are used to provide deep sedation, there is potential for unwanted residual sedation once the infusion is discontinued, resulting in delayed extubation. A major advantage of propofol over benzodiazepines is that it permits deep sedation with rapid awakening when discontinued. Patients who require prolonged ventilatory support may benefit from daily awakening with physical therapy to lessen the risk of ICU-acquired weakness, provided that weaning of sedation is not accompanied by excessive agitation or a marked increase in airway pressures.

Administration of a neuromuscular blocking agent (NMBA) is sometimes necessary. It is preferable to administer it by intermittent boluses rather than continuous infusion, because intermittent dosing permits serial assessment of the adequacy of the sedation and may lessen the risk of myopathy associated with prolonged paralysis. When sedative and opioid agents are used liberally, supplemented by intermittent NMBA boluses if needed, relatively few patients will require continuous paralysis.

Nonconventional Interventions: Heliox and Extracorporeal Life Support

Heliox is a mixture of helium and oxygen that has a lower density than air. It reduces frictional resistance when gas flow is turbulent and, by lowering the Reynolds number, encourages laminar flow. The physiologic effects of heliox are proportional to the amount of helium; no significant benefit would be expected at an $\text{FiO}_2$ above 0.4. There is relatively little data regarding the impact of heliox on lung mechanics during controlled mechanical ventilation of patients with airflow obstruction. Some investigators have reported a significant decrease in auto-PEEP when patients with COPD received heliox. In contrast, a preliminary study that administered 70:30 heliox to mechanically ventilated patients with asthma or COPD found no meaningful reduction in Pplat or auto-PEEP. Since the effects of heliox should be seen rapidly, a 30-minute trial in which indices of hyperinflation (Pplat, auto-PEEP) and $\text{Paco}_2$ are measured before and after its administration should be sufficient to assess its benefit. It is important to avoid delayed assessment, because there could be an improvement in airflow obstruction or hypercapnia due to other factors that is misinterpreted as a positive response to heliox. Heliox is expensive and its continued use is not justified when there is no clinically significant decrease in hyperinflation or $\text{Paco}_2$. Heliox sometimes leads to a modest reduction in Ppk without any change in Pplat or auto-PEEP, a response that would not justify its continuation. Due to its variable effect on ventilator operation and flow sensors, it is essential to fully understand how the particular ventilator being used is influenced by heliox.

Extracorporeal life support (ECLS) has occasionally been used for severe asthma. Acute severe asthma is fully reversible and is rarely associated with multisystem organ failure, so fulminant asthma would seem to be an ideal indication for ECLS. However, centers with considerable experience in managing fulminating asthma have reported excellent outcomes without using ECLS, indicating that it is rarely necessary. Profound, refractory, respiratory acidosis with extreme hyperinflation that limits the ability to increase minute ventilation is a reasonable indication for ECLS, especially if accompanied by barotrauma or hemodynamic instability.
A variant of ECLS has also been used for hypercapnic respiratory failure due to COPD exacerbations, both as a means to avoid intubation and to facilitate weaning. Pumpless arteriovenous and pump-driven venovenous ECLS have both been used to facilitate CO\textsubscript{2} removal in patients with COPD. Since significant CO\textsubscript{2} removal with ECLS can be accomplished with relatively low blood flows, one approach uses a -double-lumen venous catheter that is only slightly larger (15.5 F) than standard dialysis catheters. With advances in extracorporeal technology, an evolving role for ECLS in COPD exacerbation shows promise, but at this time routine adoption of this approach is premature.

WEANING
Liberating the patient from the ventilator is rarely an issue in patients with asthma. Even when airflow obstruction is fulminant at the outset, there is usually minimal residual obstruction upon resolution of the asthma exacerbation; this rarely poses a barrier to extubation. The situation in COPD is different. Unlike those with asthma, patients who are intubated for an exacerbation of COPD may have considerable derangement in lung mechanics at baseline. Even a relatively minor increase in the work of breathing, or a decrease in respiratory muscle strength, can hinder successful weaning from the ventilator.

Various methods of weaning and assessment for extubation have been used. Most often, spontaneous breathing trials are done with a low level of pressure support (≤8 cm H\textsubscript{2}O) or a T-piece trial to assess readiness for extubation. For most patients, including those with resolving asthma exacerbations, the choice of pressure support or T-piece is probably unimportant; either approach will provide a reliable test of the patient’s ability to be successfully extubated. However, the imposed work of breathing with pressure support (6–8 cm H\textsubscript{2}O) and a T-piece are not equivalent; this difference may be important for marginal patients, including those with severe COPD. One study found that more than 50% of patients who failed a T-piece trial successfully passed a spontaneous breathing trial when given 7 cm H\textsubscript{2}O and PEEP of 5 cm H\textsubscript{2}O. Compared to pressure support, a T-piece trial led to significantly greater hemodynamic and respiratory decompensation. When spontaneous breathing trials using a T-piece and pressure support are discordant, it is uncertain which method best predicts the outcome of extubation. Given the efficacy of mask bilevel positive airway pressure, extubation to this modality makes sense for some marginal candidates.

When patients with COPD repeatedly fail their daily spontaneous breathing trials despite optimal treatment of underlying airway disease, one option is to extubate to noninvasive ventilation (NIV) and then attempt to gradually wean from it. Extubation to NIV in patients who have failed spontaneous breathing trials is ultimately successful (reintubation avoided) in the majority of cases. Importantly, failure of NIV prior to initial intubation does not necessarily predict subsequent failure of NIV post-extubation. Extubation to NIV is contraindicated if there are excessive secretions, altered mentation, or hemodynamic instability, and should be used cautiously, if at all, if the patient is known to have a difficult airway.

OUTCOMES
Important outcomes associated with the use of mechanical ventilation in patients with
Mortality

Large databases that analyzed the risk of death for patients who underwent mechanical ventilation for severe asthma have reported mortality rates of 6% to 10%, while a review of single-center studies reported an average mortality rate of 8%. Some centers have reported mortality rates as low as 1% to 2%. In the majority of cases, a fatal outcome in acute severe asthma is a consequence of cerebral anoxia due to out-of-hospital cardiorespiratory arrest rather than to complications that arise in the ICU. Indeed, the risk of death is extremely low when asthmatic patients with respiratory failure are intubated without having had cardiac arrest and care is taken to limit dynamic hyperinflation. The reported mortality rates associated with invasive mechanical ventilation for COPD have varied. Recently, a mortality rate of 8.6% was found in analysis of a large database of more than 4,300 patients who underwent invasive mechanical ventilation at more than 400 hospitals nationwide. Unlike the situation with asthma, deaths in the setting of mechanical ventilation for COPD exacerbations seldom occur after cardiac arrest and are often due in part to underlying serious comorbidities or to complications related to prolonged support in the ICU.

Complications

Patients with severe asthma and COPD may experience complications common to other critical illnesses (eg, ventilator-associated pneumonia, sepsis related to indwelling catheters, or ICU-acquired delirium). Additional complications include barotrauma, hypotension, and severe myopathy.

The incidence of pneumothorax during mechanical ventilation for severe asthma in three recent large series ranged from 3% to 6%. The risk of pneumothorax increases with marked hyperinflation. Even a small pneumothorax may be catastrophic in ventilated patients with severe airflow obstruction, because intrapleural pressure will increase rapidly when hyperinflated lungs resist collapse. Clinical diagnosis of tension pneumothorax in patients with marked lung hyperinflation may be challenging. Thoracic ultrasound may aid in bedside diagnosis. Marked pulmonary hyperinflation also increases the risk of hypotension. Hypotension can also be a consequence of excessive pulmonary hyperinflation. The likely mechanism is a decrease in venous return, but increased right ventricular afterload may contribute. Rarely, the effect of hyperinflation on hemodynamics can be so extreme that it results in cardiac arrest with pulseless electrical activity. Unexplained hypotension that occurs during mechanical ventilation of a patient with severe airflow obstruction should be managed initially by disconnecting the patient from the ventilator for 30–60 seconds to assess the hemodynamic response to lung deflation.

Acute myopathy is another important complication that affects mechanically ventilated patients with asthma and COPD. Acute myopathy is characterized by severe generalized weakness affecting both proximal and distal muscles, with preservation of sensation. Some degree of diaphragm involvement may be present, but experience in patients with asthma suggests that the diaphragm is less affected than other skeletal muscles and weakness of respiratory muscles seldom causes
prolonged delays in extubation. In contrast, even a moderate degree of diaphragm impairment could impair successful weaning in patients with COPD because of the presence of residual abnormalities in lung mechanics even after the exacerbation has abated. Although not fully understood, the pathogenesis of acute myopathy in patients with severe airflow obstruction has been attributed to the combined effects of glucocorticoids and prolonged neuromuscular paralysis. However, asthmatic patients who undergo prolonged mechanical ventilation under deep sedation with minimal or no paralysis can also develop severe myopathy. In studies of both asthma and COPD exacerbations, patients who developed acute myopathy had a much longer duration of mechanical ventilation than those without myopathy, with an average duration of approximately 12 days. The need for prolonged intubation is typically a consequence of a protracted, slowly resolving severe exacerbation of asthma or COPD that necessitates moderate to deep sedation. It is very likely that near-total muscle inactivity increases risk for myopathy, regardless of whether it is accomplished by neuromuscular blockade or deep sedation. Severe weakness that occurs in the setting of an acute exacerbation of asthma or COPD may require prolonged physical therapy after extubation, but rarely leads to significant long-term disability.

REFERENCES


MECHANICAL VENTILATION IN PEDIATRIC OBSTRUCTIVE LUNG DISEASE: HOW TO MANAGE PEDIATRIC OBSTRUCTIVE LUNG DISEASE

Duane C. Williams, MD, and Bruce K. Rubin, ME, MD, MBA, FRCPC

IMPLEMENTATION AND THE NEED FOR MECHANICAL VENTILATION

Managing mechanical ventilation is one of the most important clinical skills for an intensivist. More than 60% of intensive care unit (ICU) admissions require invasive mechanical ventilator support during their stay. The decision to mechanically ventilate a patient is made when the patient’s disease leads to failure of gas exchange needed to meet the patient’s metabolic demand. Although most patients require mechanical ventilation for respiratory failure or impending respiratory failure, some are mechanically ventilated to decrease hemodynamic work during illnesses such as septicemia. Mechanically ventilating these patients improves their ability to meet the increase in oxygen demand and may prevent the development of acidosis. Infants tend to have a greater need for mechanical ventilation because of their reduced ability to generate the muscle force needed for adequate gas exchange due to the shape and lack of rigidity of the ribcage, location of the insertion of the diaphragm with less ability to descend with inspiration, reduced muscle mass, fewer type 1 muscle fibers, and lower oxidative capacity.

INVASIVE AND NONINVASIVE MECHANICAL VENTILATION IN PEDIATRIC OBSTRUCTIVE LUNG DISEASE

Anatomic Effects

Airway diseases are distinct from pleural or interstitial pulmonary diseases in that they are more common and have features that include airway obstruction, inflammation, and usually infection. Obstruction is mitigated by the supporting structures of the conducting airways, including circumferential cartilage in proximal airways and smooth muscle contraction. Each of these can be impaired by obstructive lung disease. Airway support is often decreased in the premature infant who has delayed cartilage development. This can be exacerbated by the presence of an endotracheal tube and infection leading to acquired tracheomalacia. When the endotracheal tube stent is removed, the airway narrows, which can lead to airway collapse, especially with increased intrathoracic pressure, such as during a Valsalva maneuver.

Relative lack of cartilage can also be seen when there is tracheoesophageal fistula, cartilage dysplasia syndromes (such as Williams-Campbell syndrome), and congenital airway malacia. This can also be a problem when there is extrinsic compression of the airway during development. For example, infants with vascular rings often have secondary maldevelopment of cartilage in the area of extrinsic compression. Decreasing smooth muscle tone using bronchodilators may worsen airflow obstruction in small infants; it has been proposed that cholinergic agents such
as bethanechol may improve the obstruction by increasing smooth muscle tone.2

Throughout the airway, mucus serves as a primary defense mechanism, protecting the surface from inhaled particles and bacteria, and preventing water loss at the airway surface. Mucus retention occurs when there is disruption of mucociliary clearance, mucus hypersecretion (secretory hyperresponsiveness), or narrowing of the airway, making it difficult to clear mucus at the point of narrowing.3 Mucus is readily cleared by cilia but can be trapped at the end of an endotracheal tube, because the presence of the tube impairs ciliary clearance. This is thought to contribute to ventilator-associated tracheitis and pneumonia.

The most distal, gas-exchanging airways are lined by surfactant that inhibits airway closure and reduces the pressure needed for airway opening. The very premature infant is unable to make sufficient surfactant, leading to respiratory distress syndrome of the neonate. There can also be surfactant inactivation by albumin leak or meconium aspiration. Surfactant deficiency or inactivation will predispose to atelectasis; this can be attenuated by airway surfactant supplementation.

Atelectasis is rarely due to an isolated mucus plug. The distal airways are reinflated, not by forcing air into them from more proximal airways, but rather through collateral channels, such as the alveolar pores of Kohn and bronchiolar canaliculi of Lambert.

**Delivery of Mechanical Ventilation**

Clinicians must evaluate each patient’s respiratory needs and provide appropriate care to optimize gas exchange and improve patient work of breathing (WOB). For most infants and children, this requires the use of invasive mechanical ventilation. This must be balanced against the risks of invasive mechanical ventilation, which include infection, barotrauma, discomfort, and potentially an increased use of sedating and paralytic medications. Noninvasive mechanical ventilation is commonly used in adults, and there are now interfaces and devices that offer the ability to provide noninvasive mechanical ventilation even to the smallest infants, potentially preventing the need for intubation/reintubation. There are several noninvasive means to assist patients with increased respiratory care needs.

**Noninvasive Respiratory Support, Modes, and Devices**

**HIGH-FLOW NASAL CANNULA**

High-flow nasal cannulae have been widely adopted as a means for supporting preterm infants in neonatal ICUs and more recently have become commonly used to treat infants and older children with respiratory distress or as a “bridge” to full liberation from mechanical ventilation. These patients generally receive humidified air at flows of 2 to 4 liters per minute in neonates, and to up to 50 liters per minute in adults. The amount of flow depends on the device used and the patient’s age.

**CONTINUOUS POSITIVE AIRWAY PRESSURE AND BILEVEL POSITIVE AIRWAY PRESSURE**

Similar to the increased use of high-flow therapy, the use of continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BiPAP) have recently increased. With CPAP, a positive end-expiratory pressure (PEEP) is set to decrease
both the opening pressure of airway units and the development of atelectasis. This is especially helpful when airway collapse is contributing to respiratory distress and increased WOB.

WOB can also be decreased by BiPAP, which consists of both inspiratory and expiratory positive airway pressure along with a breathing rate, set similar to pressure support invasive mechanical ventilation. The addition of inspiratory pressure will assist those patients with increased airway resistance, poor lung compliance, or hypoventilation marked by an increased partial pressure of CO$_2$. With improved synchronization capability of these devices, there has been superior delivery of breaths and improved patient comfort. Clinicians must be mindful of the patient’s level of consciousness, presence of head and facial injuries, and possible emesis when using mask CPAP or BiPAP.

**NEGATIVE PRESSURE VENTILATION**

When a person is healthy and spontaneously breathing, tidal volume is generated by making intrathoracic pressure more negative. Using a similar concept, one of the oldest forms of mechanical ventilation, dating back to the polio epidemic, was developed in the form of the iron lung. Negative pressure ventilation (NPV) can be triggered by diaphragm or vagus nerve pacing, via hard cuirass shells sealed around the chest (ie, miniature iron lungs). Although not generally as effective as noninvasive devices that deliver positive pressure ventilation, once a closely fitted circuit is obtained, the vest can assist with ventilation while not obscuring the face. In patients with upper airway obstruction or pharyngeal collapse, NPV can worsen upper airway obstruction, similar to that seen with obstructive sleep apnea.

**Invasive Modes and Devices**

When the decision is made to move to invasive mechanical ventilation, the clinician must balance the need to provide adequate oxygenation and ventilation assistance with the risk of ventilator-induced lung injury. With conventional mechanical ventilation (CMV), the ventilated breath is provided by either pressure-controlled or volume-controlled ventilation. The duration of the breath in both cases is determined by the inspiratory time setting.

**PRESSURE-CONTROLLED VENTILATION**

With pressure-controlled ventilation, the pressure setting limits the pressure delivered by the ventilator to reduce the risk of barotrauma (Figure 1A). Modes that provide pressure-controlled ventilation include pressure control, synchronized intermittent mechanical ventilation (SIMV) with a pressure limit, pressure-regulated volume control, and pressure support ventilation.

**VOLUME-CONTROLLED VENTILATION**

With volume-controlled ventilation, a constant flow pattern with a set-delivered volume limit can mitigate the risk of volutrauma (Figure 1B). Modes that provide volume-controlled ventilation include volume control, SIMV with a pressure limit, and volume support.

*Figure 1.* Flow versus time for pressure (A) and volume (B) controlled delivered mechanically ventilated breaths
Setting the Conventional Ventilator

Ventilator settings and changes should be made in conjunction with the respiratory therapist and, when possible, using flow graphics to ensure that the settings meet the patient’s needs for adequate and safe gas exchange.

**POSITIVE END-EXPIRATORY PRESSURE**

PEEP can decrease inflation pressure and help prevent alveolar collapse at the end of exhalation. Initially, this value is often set at 5 cm H$_2$O; however, it is probably preferable to set it at 2 or 3 cm H$_2$O above the airway collapse pressure. This point can be seen on the pressure-versus-volume graphic loop denoted as the lower inflection point (Figure 2). With proper lung recruitment, oxygenation, and pulmonary compliance, ventilation should improve. Maintaining effective PEEP also decreases intrapulmonary shunting of blood and improves arterial oxygenation.

**Figure 2.** Volume versus pressure
PEAK INSPIRATORY PRESSURE AND PLATEAU PRESSURE

Depending on the ventilation mode, the peak inspiratory pressure (PIP) will either be set (pressure control) or will vary to deliver a specific volume (volume control). Flow graphics can usually identify an increase in both PIP and plateau pressure, which are associated with an increased risk of mortality, as these generally demote worsening pulmonary compliance and/or increasing airway obstruction.4

TIDAL VOLUME

Tidal volume is the volume of air provided to the patient with each breath. Following the Acute Respiratory Distress Syndrome (ARDS) Network data linking tidal volumes greater than 7 mL/kg to mortality, there has been an effort to limit tidal volume to the lowest value that is effective. With pressure-controlled ventilation, tidal volume can vary with compliance, so a cuffed endotracheal tube may help ensure an adequate delivered tidal volume, especially in the presence of poor pulmonary compliance.5 With volume-controlled ventilation, the clinician sets the desired tidal volume while ensuring that the peak and plateau pressures are at a minimum, in an effort to reduce the risk of barotrauma and ventilator-induced injury.

RESPIRATORY RATE

Minute ventilation is the product of tidal volume and respiratory rate. Together, these largely determine ventilation, defined as CO₂ elimination. Although there are normal ranges for age, the patient’s illness may require adjusting these to meet metabolic needs. If there is concern for air trapping, the rate may need to be decreased to provide sufficient time to exhale completely (Figure 3).

Figure 3. Flow versus time graph
Inhalation represented by the upward deflection with exhalation represented by the downward deflection. (B) illustrates the finding of air trapping (see arrows). (C) illustrates changes with a decrease in inspiratory time. (D) illustrates changes with a decrease in respiratory rate.

**INSPIRATORY TIME**

Inspiratory time is the time, in seconds, the respiratory cycle spends in inspiration (Figure 1). Increases in inspiratory time may improve oxygenation but can negatively affect ventilation. This is most prominent in a mode such as airway pressure release ventilation (APRV), which will be discussed later (Figure 4). An illness with air trapping, such as severe asthma, may need a shorter inspiratory time to allow enough time to exhale (Figure 3C). A process that causes profound hypoxemia may require a longer inspiratory time for effective oxygenation. With a respiratory rate of 20 breaths per minute, the respiratory cycle is 3 seconds (60 divided by 20); therefore, an inspiratory time of 1 second will provide the patient 2 seconds to exhale. If the respiratory rate is then increased to 40 breaths per minute, the respiratory cycle is now 1.5 seconds. With no change in the inspiratory time, an exhalation time of 0.5 seconds may not be adequate.

*Figure 4.* Difference in pressure versus time between conventional mechanical ventilation (A) and airway pressure release (B)
Adjuncts to ventilator support can assist in both ventilation and oxygenation. Heliox is sometimes used in mechanically ventilated patients for obstructive airway disease, such as asthma. Low-density gases such as heliox may also decrease peak airway pressure and resistance in pediatric ARDS. Because nitrogen is a less dense gas, CO₂ diffuses four to five times faster through helium than through nitrogen (air).

### High-Frequency Ventilation

High-frequency ventilation (HFV), generally defined as a breathing rate of more than 150 breaths per minute (2.5 Hz), is another mode of ventilation to assist patients with respiratory failure refractory to conventional ventilation. It may also decrease the pressure swings associated with barotrauma. Theoretically, the advantage of HFV is that it maintains an open-lung approach with the use of relatively higher mean airway pressure (MAP) but low phasic volume and pressure changes, thereby keeping the airway open between the lower and upper inflection points (Figure 2).

This limits airway trauma (atelectrauma) caused by the opening and closing of the lung to deliver a tidal volume, as well as lung overdistention (volutrauma), especially in the presence of poor compliance (Figure 5). However, there are no clear data to support HFV’s superiority to conventional ventilation, and some studies suggest that HFV may even worsen outcomes.

**Figure 5.** Difference in the effects of poor lung compliance on the volume versus pressure loop
Note the migration of the lower inflection point.

The terminology used to describe HFV is different, as flow is delivered and pressure maintained in a different manner than conventional ventilation. With the transition from CMV to HFV, the MAP is initially set at 3 to 5 cm H$_2$O above the MAP measured during conventional ventilation. In some unstable patients and in those with intravascular volume depletion, the increase in MAP may decrease venous return to the heart such that the patient may need additional intravenous fluids to compensate.

There are several methods of delivering HFV. High-frequency oscillatory ventilation (HFOV) uses a piston assembly propelled by changing polarity of a square driver attached to a diaphragm. This piston motion is another crucial distinction between HFOV and CMV, in that both phases of the respiratory cycle are active, generating a tidal volume in the range of 1 to 2 mL/kg. Because of this, HFOV should probably not be used when there is high airway resistance (eg, asthma) because air trapping may increase in ventilated parts of the lung, placing the patient at risk of air leak and worsened ventilation, although atelectasis may increase in poorly ventilated areas.

The Bunnell high-frequency jet ventilator (Bunnell, Inc.) operates in conjunction with a conventional mechanical ventilator. With the jet ventilator, a Bunnell Life Pulse device is used to interrupt flow via a pinch valve to generate a stream of high-frequency pulses. This allows for smaller tidal volumes to be delivered at a higher positive end-expiratory level but in a state that limits volutrauma. Gas flows into the lungs at a high velocity (Figure 6). The conventional ventilator works in tandem with the jet ventilator to generate the MAP for the jet ventilator by manipulating PEEP and providing sigh breaths for lung volume recruitment (Figure 7). Unlike HFOV, exhalation on the jet ventilator is passive from elastic recoil. Furthermore, delivery of gas at high velocity into the airways allows exhalation to occur slowly, with the potential for more complete emptying, as noted in Figure 6. In the figure, inspired gas flows down the center of the airways so the path of least resistance for exhaled gas is against the airway walls, as shown in the adjacent figure. Theoretically, this may improve mucus clearance. Jet ventilation has been regarded as the safest way to mechanically ventilate a patient with an air leak, such as after surgery.
as a bronchopleural fistula. The Bunnell high-frequency jet ventilator can be used in patients who weigh up to 15 kg, although the exact weight cutoff depends on chest size and degree of lung injury.

**Figure 6.** Inhalation and exhalation jet streams seen with high-frequency jet ventilation

![Diagram of high-frequency jet ventilation](image1)


**Figure 7.** Mechanically delivered breaths with high-frequency jet ventilation

![Diagram of high-frequency jet ventilation](image2)

Note the delivered mechanical “sigh” breath of the conventional ventilator.

**Setting High-Frequency Oscillatory Ventilation**
**MEAN AIRWAY PRESSURE**

Unlike the conventional ventilator, where MAP is increased by changing inspiratory time, PEEP, tidal volume, and PIP, with HFOV, the desired MAP is directly set, usually at 3 to 5 cm H$_2$O above that used for the conventional ventilator to facilitate gas delivery to the distal airways. Care must be taken not to overdistend the lungs; this can usually be assessed by chest radiograph. When the desired oxygenation is reached, inspired oxygen concentration can be decreased to 0.50, and then MAP can be decreased (Figure 8).

*Figure 8.* Mechanically delivered breaths with high-frequency oscillatory ventilation

Note the shaded area depicts the mean airway pressure. The time between each deflection is denoted by the hertz. The degree of the deflection is depicted by the amplitude.

**FREQUENCY (MEASURED IN HERTZ OR BREATHS PER MINUTE)**

HFV is defined as providing a respiratory rate of greater than 150 breaths per minute (2.5 Hz) with small tidal volumes. The breath frequency on HFV is directly set. Up to a limit, the higher the rate, the more the lung may be protected from pressure swings. As an initial setting, young children are routinely started on HFOV at a frequency of 8 to 10 Hz.\textsuperscript{10}

**AMPLITUDE (POWER)**

Adjusting the amplitude of each breath on HFOV provides the amount of sinusoidal deflection around the set MAP to ventilate the patient (Figure 8). Without amplitude, the ventilator is delivering PEEP. Initially the amplitude is increased until there is visible motion of the thorax (adequate “jiggle”). It is important to recognize that, at peak deflection (trough of the amplitude wave), some alveoli may collapse, especially in young patients, and this can worsen gas exchange (Figure 9).

*Figure 9.* High-frequency oscillatory ventilation breath parameters
(A) The result of increasing the amplitude with high-frequency oscillatory ventilation (HFOV). (B) The result of increasing the hertz. With smaller under the curve there will be a decreased minute ventilation and ability to ventilate. (C) With an increase in frequency, there will be an increase in the area under the curve, which will improve minute ventilation, however sacrificing the protective aspects of HFOV.

**INSPIRATORY TIME**

Given the high respiratory rate, the inspiratory time is usually set at 1:2 (or 33%).
Rarely will this be changed to, or less than, 1:1 (or 50%) because, although there will be an increase in tidal volume delivery, air trapping can worsen with an associated increased risk of airway trauma.

**BIAS FLOW**

Bias flow is the gas flow through the circuit, and is generally maintained at the lowest possible level to meet the desired MAP and amplitude. Bias flow settings are somewhat dependent on the ventilator used. It is often set at approximately 40 L/min but may be increased to 60 L/min.10

With HFV, oxygenation is primarily affected by MAP and inspired oxygen concentration, while ventilation is affected by amplitude and frequency. However, increasing the frequency may decrease the tidal volume (Figure 9B), while decreasing the frequency might improve ventilation at a cost of increased risk of airway volutrauma (Figure 9C).

**Setting High-Frequency Jet Ventilation**

**MEAN AIRWAY PRESSURE AND PEAK INSPIRATORY PRESSURE**

As with HFOV, the MAP should generally be set at a level 3 to 5 cm H₂O above that of the conventional ventilator for patients with poor pulmonary compliance. However, to set the MAP also requires adjusting the PEEP of the conventional ventilator. The PIP on the jet ventilator is set to ensure that there is adequate thoracic movement (Figure 10).

*Figure 10.* High-frequency jet ventilation pressure
(A) The mechanically delivered breaths with high-frequency jet ventilation (HFJV). (B) The result of increasing peak inspiratory pressure (PIP). Note the increased area under the curve and improved minute ventilation. (C) The result of increasing the positive end expiratory pressure (PEEP). Note: with HFJV once max PIP is reached, further increases in your PEEP will decrease the area under your curve and thus minute ventilation.

**FREQUENCY/RATE**

When using the jet ventilator, it is generally reasonable to start at a frequency of 6 Hz (360 breaths per minute). Increasing the frequency will generally improve ventilation but may also increase air trapping. Air trapping can be assessed by determining whether the difference in the PEEP set on the conventional ventilator and that measured by the jet ventilator is greater than 2 cm H$_2$O.

**INSPIRATORY TIME**

Initial inspiratory time is set at 20 milliseconds (0.02 sec). The inspiratory-to-exhalation time ratio depends on changes in frequency. With increasing frequency, but no change in set inspiratory time, the inspiratory-to-exhalation time
ratio will increase, and the shorter exhalation time can inadequately empty airways with longer time constants, predisposing to atelectasis.

**SERVO PRESSURE**

Servo pressure is the amount of pressure the jet ventilator must generate to achieve the set PIP. It ranges from 0 to 20 pounds per square inch. Therefore, with improving compliance and decreasing resistance, the servo pressure will increase. It can also increase, often fairly quickly, when a patient develops an air leak, such as a pneumothorax (until it becomes a tension pneumothorax). Contrarily, worsening compliance and airway obstruction will cause servo pressure to decrease.

**Neurally Adjusted Ventilator Assist**

Neurally adjusted ventilator assist (NAVA) is currently available only on the Servo-i ventilator (Maquet Getinge Group). NAVA provides proportional pressure support based on measurements of the electrical activity of the diaphragm (EAdi), which serves as a proxy for the neuronal output of the respiratory center. Because this electrical activity is generated by the patient at the start of inspiration, NAVA can decrease patient-ventilator breathing asynchrony. To initiate NAVA, a catheter is placed in the esophagus containing an electrode that detects an EAdi signal. A signal may not be detected in patients with some anatomic defects (eg, diaphragmatic hernia), central apnea without respiratory drive (sedation, brain damage), or in the absence of electrical diaphragmatic action (phrenic nerve damage, muscle relaxants). It is important to set the apnea backup in the event that the reference electrode of the NAVA catheter does not receive a signal.

**Setting Neurally Adjusted Ventilator Assist**

Once the ventilator detects an EAdi signal of greater than 0.5 µV (known as the trigger EAdi), it will commence ventilation to a preset NAVA level (denoted in cm H₂O/µV). An increase in the EAdi min denotes a need to increase PEEP, while an increase in the EAdi max denotes a need for an increase in the NAVA level. Lowering the NAVA level increases the intrinsic impulse needed from the diaphragm to trigger the ventilator. Similar to the flow trigger used with conventional mechanical ventilators, an increase or decrease in this signal strength can affect patient-ventilator synchrony; thus, the level is titrated to patient effort. Too high a level decreases the amplitude of the EAdi max signal and will lead to excessive pressure delivery and the potential for ventilator-induced lung injury. A low NAVA level will result in a high EAdi max signal as a sign of respiratory distress, usually associated with increased effort, retractions, nasal flaring, and tachypnea. As the patient improves, the EAdi max will decrease and the NAVA level can be decreased. Data suggest that the use of NAVA is associated with a decrease in PIP, improved patient-ventilator synchrony, and a decrease in the duration of ventilator support in neonates with ARDS.

**Airway Pressure Release Ventilation**

APRV allows for spontaneous breathing throughout all phases of the machine-imposed respiratory cycle. APRV is a pressure-limited, time-triggered, and time-
cycled mode that maintains an elevated baseline pressure with deflections of gas during a lower setting ($P_{low}$) (Figure 4).

APRV is designed to maintain most of the ventilator time cycle at the level of $P_{high}$ to promote lung recruitment and thus oxygenation. Given this length of time of the cycle at $P_{high}$, ventilation is achieved with a combination of spontaneous breaths and mandatory breaths generated by the cyclic changes between $P_{low}$ and $P_{high}$. Usually, $T_{low}$ is set short enough that $P_{low}$ is not reached. Given the time spent at $P_{high}$, APRV may be beneficial in a situation in which HFV is not possible or not preferred. Because of the passive flow with APRV compared to HFV, the patient will likely be more comfortable, have better synchrony, and need less pharmacologic sedation.

**Setting Airway Pressure Release Ventilation/Bilevel**

**PRESSURE HIGH AND PRESSURE LOW**

With transition from a conventional ventilator mode, $P_{high}$ is set at a level 3 to 5 cm H$_2$O above the previous mean arterial pressure. $P_{low}$ is generally set at 0 to 5 cm H$_2$O.

**TIME HIGH AND TIME LOW**

Initially, most clinicians set $T_{high}$ in a range of 4 to 6 seconds and adjust as needed for oxygenation and ventilation goals. The longer the $T_{high}$ (time spent at $P_{high}$), the better oxygenation is, but at the expense of ventilation. $T_{low}$ is set in the range of 0.3 to 1 second and is adjusted for a target of 25% to 75% of peak expiratory flow. Lengthening $T_{low}$ improves ventilation at the expense of oxygenation and increases the risk of atelectasis.

**SPECIFIC DISEASE MANAGEMENT AND ASSESSMENT OF EFFECTIVE CARE**

**Specific Disease Management**

Asthma is a disease of reversible airflow obstruction due to inflammation, bronchospasm, and mucus hypersecretion and retention. In children, the inflammation associated with acute asthma exacerbations is usually due to a respiratory virus infection on a background of an allergy driven by T helper cells type 2. Most acute asthma episodes, in both children and adults, are precipitated by respiratory viruses. Among these, the human rhinovirus C is most frequent and most severe. Asthma precipitated by rhinovirus C is indistinguishable from other forms of asthma.

Asthma can also be triggered by cold dry air, exercise, tobacco smoke, or exposure to allergens. Most children with asthma have allergic manifestations, including increased IgE and eosinophils, exhaled nitric oxide, and T helper cell type 2 cytokines. Among these cytokines, interleukin-13 drives mucous cell metaplasia, leading to increased production and poor clearance of airway mucus that is resistant to steroid therapy. Most children who die with asthma die by drowning in these secretions. Without correction, the patient will develop air trapping, leading to poor ventilation, and progressing to respiratory acidosis which in turn may impair cardiac output.
Noninvasive ventilation has been successfully used in patients with severe asthma and may decrease the risk of dynamic hyperinflation occurring with mechanical ventilation. If invasive mechanical ventilation is required, it is recommended that low PEEP be used and that pressure-controlled ventilation with long exhalation times be used to allow emptying of airways, which have long time constants.

Mechanical ventilation in asthma increases the risk of air leak and barotrauma. Up to 30% of patients who have a life-threatening asthma exacerbation (ie, requiring care in an ICU) require mechanical ventilatory support. Severe asthma leads to air trapping seen on mechanical ventilation with the flow-versus-time graphic (Figure 3). In comparing Figure 3A to Figure 3B, note that there is a failure to return to baseline during exhalation. Pulmonary hyperinflation is a cause of hypotension and barotrauma, which may be mitigated by noninvasive ventilation. To accomplish this, the inspiratory time can be decreased to allow a longer exhalation time (Figure 3C) as long as the change in inspiratory time does not also decrease the MAP and oxygenation. It is also possible to decrease the respiratory rate to allow for a longer exhalation time (Figure 3D). For the most part, the management for ventilated asthma patients is high tidal volume with a low rate, which ensures adequate minute ventilation but allows time to exhale, coupled with fast weaning from the ventilator. The combination of lower rate, higher tidal volume, and lower PEEP may be uncomfortable for the patient, who may require the addition of sedation and muscle relaxation. Given the desire to minimize ventilator-induced lung injury caused by overdistension, in the absence of known cardiac disease, permissive hypercarbia targeting a pH of greater than 7.2 allows for the use of lower tidal volumes, minimizing volutrauma. As air trapping improves, it should be possible to fairly rapidly reduce the inspiratory pressure and increase PEEP to prevent airway collapse.

Bronchiolitis is associated with inflammation of the small airways. In infants, it is caused by respiratory viruses, predominantly the respiratory syncytial virus (RSV). All infants are exposed to RSV in their first years of life and, for most, it is a mild respiratory infection. However, some patients have more severe disease, leading to hypoxemia, ventilation perfusion mismatch, and atelectasis. The secretions in RSV bronchiolitis are rich in polymeric DNA and, like asthma, can obstruct the distal airways. Bronchiolitis is a clinical syndrome and is not strictly defined by the presence or absence of RSV. As with asthma, mechanical ventilation of infants with bronchiolitis carries significant risks and is associated with air trapping and barotrauma. Unlike asthma, medications such as bronchodilators or corticosteroids have no place in therapy; they are ineffective and their use is associated with adverse effects.

Cystic fibrosis (CF) affects approximately 1 in 3,500 Caucasian births but is also common among the African American and Hispanic populations. There are approximately 70,000 people with CF worldwide today. It is caused by abnormalities in the CF transmembrane conductance regulator (CFTR) gene and protein. The CFTR ion channel helps regulate chloride, water, sodium, and bicarbonate transit across the airway epithelium into the airspace. In CF, CFTR dysfunction leads to low-volume secretions that can be difficult to clear, causing obstruction, stasis, exaggerated airway inflammation, and persistent airway infections with biofilm containing bacteria such as Staphylococcus aureus and Pseudomonas aeruginosa. Management of CF includes providing adequate nutrition, digestive pancreatic enzymes, antibiotics for treating infection, immunomodulatory medications, and
airway clearance therapies.

Because CF is a chronic progressive obstructive airway disease, the need for mechanical ventilation with significant hypoxemia and CO$_2$ retention usually is associated with cor pulmonale and a poor prognosis. Patients on mechanical ventilation are considered poor risks for lung transplantation in most medical centers. Therefore, many medical centers institute invasive mechanical ventilation only in those CF patients who have an acute severe deterioration that is potentially reversible. However, it is becoming increasingly common to use noninvasive mechanical ventilation, such as BiPAP, to improve quality of life in patients with end-stage CF lung disease.

Pneumonia is defined as an acute infection of the lower airways. In children, most pneumonia is caused by respiratory viruses and, while the typical virus rarely produces respiratory failure requiring mechanical ventilation, this can occur with infections due to adenovirus, influenza virus, and occasionally other viruses, especially in the immunocompromised host. Viruses can be devastating in the immunocompromised host. Mechanical ventilation may be used to support these patients while their immune system is reconstituted.

Bacterial pneumonia is less common than viral pneumonia. Mycoplasma can produce seasonal “walking pneumonia” in healthy school-aged children but few develop respiratory failure requiring mechanical ventilation. Gram-positive organisms, in particular Staphylococcus aureus, can produce severe pneumonia and, when associated with the production of virulence factors, can cause pneumonia and respiratory failure with parapneumonic effusion and necrotizing pneumonia.

Treatment of pneumonia entails identifying the organism by obtaining cultures from the airway, pleural fluid, and blood, and providing antibiotics with supportive care. Patients with severe pneumonia can have hypotension, demonstrate inappropriate antidiuretic hormone secretion with fluid retention, and develop cytokine storm with ARDS. Most patients with pneumonia and parapneumonic effusion or empyema do not require chest tube drainage of the effusion, and those with slowly resolving complex parapneumonic infusions will benefit equally from the installation of fibrinolytic medications, such as urokinase, and from thoracoscopic debridement of the loculations. An important caveat is that children who have necrotizing pneumonia should almost never have a chest tube inserted. Prolonged treatment with appropriate antibiotics will lead to complete resolution of the necrotic pneumonia in most children, while insertion of a chest tube has been associated with the development of persistent air leaks and lung damage. Therefore, because of the risk of bronchopleural fistula, we recommend against the insertion of a chest tube in children with documented necrotizing pneumonia.

The presence of a tension pneumothorax in the setting of necrotizing pneumonia (not just pleural effusing or abscess) strongly suggests the development of a bronchopleural fistula. We strongly urge the clinician to obtain confirmation that the air is under tension by needle aspiration (not just mediastinal shift). If air is present, a very small, soft chest tube can be inserted and allowed to drain the air under water seal, but not under vacuum because this may exacerbate the problem. We also suggest that the tube be removed as soon as it is clear that air is evacuated and it stops bubbling.
Although patients with pneumonia or bronchiectasis have been treated with both systemic and aerosol antibiotics, there are no convincing data showing that the addition of aerosol antibiotics improve outcomes. Also, there are no data demonstrating that mucolytics, such as acetylcysteine or dornase alfa, improve outcomes in patients with asthma or pneumonia who require mechanical ventilation. Unless the patient is known to have underlying asthma, there is no proven role for aerosol bronchodilators or corticosteroids in the treatment of acute pneumonia. There is also no evidence that chest physical therapy or airway clearance devices will aid in the resolution of either pneumonia or atelectasis.

Pediatric ARDS, similar to ARDS in adults, can be the end result of a number of underlying insults, including trauma, severe pneumonia, toxic ingestion or inhalation, or severe nonpulmonary infection. Any of these can trigger a systemic immune response syndrome leading to a cytokine storm and widespread inflammatory activation with failure to resolve inflammation before significant tissue damage ensues. The lung is particularly vulnerable to this cytokine storm, which can progress to ARDS with surfactant inactivation, atelectasis, severe inflammation, and associated multigorgan system failure. Patients with ARDS are at risk of fluid overload, barotrauma and volutrauma, and secondary infection. Management of ARDS can be challenging, with a significant number of patients requiring support beyond mechanical ventilation to include extracorporeal membrane oxygenation (ECMO). Even with optimal care, pediatric ARDS carries a fairly high mortality rate of 20%. However, this is less than half the mortality rate reported for adults with ARDS.

The most effective way to mechanically ventilate a patient with pediatric ARDS is controversial due to a lack of randomized controlled trials and the wide age range (and thus anatomic differences) in the pediatric population. In 2000, the ARDS Network published data showing that a targeted tidal volume of 6 mL/kg compared to 12 mL/kg in adult patients decreased mortality and, with each mL/kg tidal volume above 6 mL/kg, there was a greater risk of developing ventilator-induced lung injury. With these data, most intensivists have adopted low tidal volume ventilation strategies in the pediatric population, while optimizing PEEP to allow for adequate surface area for gas exchange. Furthermore, allowing for permissive hypercapnia along with an oxygen saturation goal set from 88% to 92% has also been adopted. Long-term follow-up data for children ventilated with ARDS have not been published; however, in adults there is an unclear risk of developing chronic lung disease. At the Pediatric Acute Lung Injury Consensus Conference several recommendations were developed specifically for pediatric management of ARDS in an effort to provide consistency of care and a platform for future research endeavors.

**Patient Monitoring with Mechanical Ventilation**

Mechanical ventilation may exacerbate lung injury and inflammation. It is important to monitor patient-ventilator interactions to minimize the severity of ventilator-induced lung injury while providing the assistance needed.

**END-TIDAL CARBON DIOXIDE**

End-tidal CO₂ is defined as the peak airway CO₂ value during exhalation. It is dependent on adequate pulmonary capillary flow of CO₂-rich blood to alveoli. This
may be impaired in the presence of cardiac dysfunction or atelectasis. The normal end-tidal CO\textsubscript{2} in a healthy subject is generally less than 5 mm Hg different from the partial arterial CO\textsubscript{2} pressure, representing the normal anatomic dead space of the upper airway. Changes in end-tidal CO\textsubscript{2} may occur more rapidly than changes in peripheral oxygenation as measured by pulse oximetry.

**SYSTEMIC BLOOD PRESSURE**

With intravascular volume depletion, a change in intrathoracic pressure may affect venous return and thus cardiac output. Furthermore, the anesthetics used during tracheal intubation can lower systemic vascular resistance, which decreases blood pressure, and potentially impairs end-organ perfusion.

In diseases such as severe asthma, the increase in intrathoracic pressure can decrease venous return, leading to pulsus paradoxus, an exaggerated variation in systolic blood pressure during inspiration. Normally, the difference in systolic blood pressure during inhalation and exhalation is less than 10 to 15 mm Hg. However, as increased thoracic pressure decreases venous return, there can be a concomitant fall in systolic blood pressure. This may be partially offset by the associated decrease in the afterload on the left ventricle. Patients may need added preload to meet end-organ perfusion needs until the acute respiratory process has improved. Additionally, high lung volumes can cause an increase in pulmonary vascular resistance (**Figure 11**) and reduce delivery of preload from the right ventricle to the left atrium.

**Figure 11.** Pulmonary vascular resistance (PVR) as it relates to lung volume

![Pulmonary vascular resistance](image)

Note as you move away from functional residual capacity in either direction, there is an increase in PVR.

**AIRWAY GRAPHIC PATTERNS**
Many modern mechanical ventilators (Avea, CareFusion Corporation; Servo-i, Maquet Getinge Group; Dräger) have flow and volume sensing capabilities that allow the clinician to assess airway mechanics both over time and on a breath-by-breath basis. The former help the clinician assess the inertia or progress of the disease, while the latter are extremely valuable for immediately evaluating the effects of changing ventilator settings on the patient’s airway dynamic physiology (Figure 2).

**PRESSURE-VOLUME PATTERN**

The pressure-volume loop provides the ability to assess the pressure needed to generate a given tidal volume (Figure 2). As airway pressure is increased, lung compliance initially improves, facilitating lung inflation. However, inflating the lung further reduces lung compliance at the end of inflation. The lower inflection point reflects the point of alveolar recruitment, while the upper inflection point is thought to correspond to alveolar overdistention. PEEP is set at or slightly above the lower inflection point; this is especially pertinent in the presence of ARDS.

**FLOW DELIVERY PATTERN**

The flow/time airway scalar provides insight into the inspiratory and expiratory phases of the respiratory cycle. The difference in selection of a pressure- or volume-controlled breath will also affect the manner in which flow is delivered (Figure 1). The variable decelerating flow pattern seen with a pressure-controlled breath results in a more rapid rise in airway pressure during the initial phase of inspiration compared with the volume-controlled breath. The variable decelerating flow is higher than the constant flow pattern seen with the volume-controlled breath and thus generates a lower PIP related to improved gas delivery as well as a flow pattern that may better match the patient’s inspiratory demands. Additionally, the initial high flow used to reach the set pressure limit with the pressure-controlled breath is thought to be potentially beneficial in opening stiff alveoli in conditions such as ARDS or surfactant deficiency, promoting better gas exchange and improving the distribution of ventilation among lung units with heterogeneous time constants. Because of this, pressure-controlled ventilation mode is usually chosen for patients with poor compliance. To date, there are no data showing an outcome difference between the different control methods of mechanical ventilation.

Flow asynchrony occurs when the flow provided by the ventilator does not meet the patient’s needs. Notably, in volume-controlled ventilation, delivered flow is fixed, while in pressure-controlled ventilation, flow is variable.

**INADEQUATE TRIGGER**

The ease by which a patient signals to the ventilator that a breath is needed is mitigated via a set flow or pressure trigger. Flow triggering is generally more sensitive than pressure triggering, since a small change in flow requires less inspiratory effort than a change in pressure. In infants, poor trigger sensitivity is the most common cause of patient-ventilator asynchrony. Also, a leak in the ventilator system is perceived by the ventilator as a desire to initiate a breath and results in excessive triggering, known as autocycling.

**PATIENT-VENTILATOR ASYNCHRONY**

Patient asynchrony and discomfort (often noted as “fighting the ventilator”) can
prevent liberation from mechanical ventilation. Providing inadequate ventilator support to meet the patient’s needs leads to tachypnea, nasal flaring, retractions, and patient discomfort. These symptoms are sometimes treated with sedation medications and possibly muscle relaxation, but these measures can prolong the need for mechanical ventilation. To improve patient-ventilator synchrony, clinicians must assess whether an abnormality of the patient-ventilator interaction is causing the distress.

MEDICAL THERAPY USED WITH MECHANICAL VENTILATION

Bronchodilators, Mucolytics, and Surfactants

Bronchodilators and asthma medications are effective therapy for asthma. These medications have not been shown to be effective for the treatment of other pulmonary diseases leading to respiratory failure. The beta-agonist bronchodilators act by relaxing airway smooth muscles, but the use of large amounts of beta-agonists, either systemically or by inhalation, can lead to hypokalemia, hyperglycemia, and cardiac strain. Toxicity from beta-agonists is dose dependent, while effectiveness plateaus. Patients with severe asthma who receive large amounts of beta-agonists may also have downregulation of the beta receptor leading to attenuated beneficial effects. There are few data suggesting that systemically administered beta-agonists are more effective than inhaled beta-agonists, even in patients with severe asthma. The use of intravenous beta-agonists comes at a cost of significantly greater toxicity.

Surfactants have been successfully used to treat premature newborn infants with surfactant deficiency and respiratory distress syndrome. Although severe lung disease and ARDS are associated with surfactant inactivation, studies of aerosol or endotracheal administration of surfactant in these patients who are mechanically ventilated have produced disappointing results. Surfactants have the ability to stabilize the alveolus and also appear to aid in secretion clearance by decreasing adherence of secretions to the airway wall. This is in contradistinction to mucolytics such as acetylcysteine or bicarbonate, which have been used unsuccessfully, by installation or inhalation to thin secretions. There are no clear data suggesting that surfactants or mucolytic drugs are effective in treating children with respiratory failure who require mechanical ventilation.

Corticosteroids are extremely effective in treating asthma and show positive results in severe ARDS. Toxicity, such as adrenal suppression, is dose dependent. Although systemic corticosteroids are often administered up to four times a day, there are no published data that show additional benefit to giving systemic corticosteroids more frequently than twice a day even in the most severely ill children with asthma who require mechanical ventilation. The maximum dose to be administered should be 2 mg/kg or up to 60 mg per day either given once or divided twice per day. There is no advantage to giving higher amounts of corticosteroids because this increases the risk of hyperglycemia, hypertension, and adrenal suppression.

Antibiotics are uniformly administered for the treatment of patients with severe pneumonia who require mechanical ventilation and are also frequently used to treat patients with other severe lung diseases (eg, pediatric ARDS) because of uncertainty about the involvement of bacterial infection in the pathogenesis of the disease. Aerosolized antibiotics have been used for more than 60 years, but antibiotics
developed specifically for aerosol use have only been introduced in the past two decades. There is a wealth of information regarding the routine use of aerosolized antibiotics to suppress the chronic lung infection in CF but far fewer data exist supporting their use in mechanically ventilated patients.

**EXTRACORPOREAL MEMBRANE OXYGENATION**

ECMO has been successfully used to manage unremitting pediatric respiratory failure that does not adequately respond to mechanical ventilation. Data suggest that the early initiation of ECMO may decrease the risk of lung injury associated with high-pressure (or high-volume) mechanical ventilation.

**HOME VENTILATION**

Home mechanical ventilation has been used for several decades to treat select children and adults with chronic respiratory failure. These include patients with neuromuscular diseases, such as muscular dystrophy, spinal motor atrophy, and mitochondrial myopathies, as well as those who have sustained spinal cord trauma leading to diaphragmatic dysfunction and, as previously noted, in some patients with chronic progressive respiratory failure. Home mechanical ventilation can be noninvasive, using face mask or nasal devices to deliver bilevel pressure support mechanical ventilation, or via negative pressure devices.

Some patients, notably those with congenital central hypoventilation syndrome, have had diaphragmatic pacers implanted to permit effective ventilation during periods when there is loss of central control of ventilation. These modalities should be targeted to specific populations. For example, although NPV can be considered less invasive than positive pressure ventilation via a tracheostomy, it is unsuitable for patients with upper airway collapse since this would limit its effectiveness. Additionally, the apparatus can be uncomfortable and can lead to skin breakdown, especially in patients with decreased mobility. In a similar fashion, diaphragmatic pacing is best suited for those patients with central apnea or a muscular failure of diaphragmatic function as opposed to those with myopathies and weakness.

Positive pressure ventilators for home use have become smaller, more robust, and now have more features that include newer modes of ventilation, including NAVA, and the introduction of flow graphics, which allow for more accurate assessment of the effectiveness of mechanical ventilation over time in an individual patient.

**KEY POINTS**

- Mechanical ventilation, in a variety of forms and modes, is a well-accepted means of supporting critically ill children with respiratory failure.
- Although pediatric data are limited, there have been advancements in care that have allowed for improvement in outcomes.
- There remains a substantial need for additional research to ascertain how the delivery, methods, and various associated therapies of mechanical ventilation will provide the best results for pediatric patients.

**REFERENCES**

DISEASE-SPECIFIC STRATEGIES FOR MECHANICAL VENTILATION OF NEWBORNS

Donald Null Jr, MD

Objectives

- Understand how the neonate’s lung differs from pediatric and adult patients
- Understand the pathophysiology of various lung disorders of the neonate
- Understand the appropriate ventilator setting for both conventional and high frequency ventilators for various pathophysiology of lung disorders in neonates

INTRODUCTION

The use of various forms of respiratory support for neonates who do not require endotracheal intubation has increased dramatically in the past 10 to 15 years. Also, a significant number of neonates require intubation for assisted ventilation. Because these patients have frequently failed less invasive forms of support—continuous positive airway pressure (CPAP), humidified high-flow nasal cannula, bilevel positive airway pressure, nasal intermittent positive-pressure ventilation, and high-frequency nasal ventilation—their lung disease is generally more severe. The term less invasive, rather than noninvasive, is preferred since all of these modes have complications.

The management of neonates requires a solid understanding of the pathophysiology of the lung disorders being treated. An understanding of how each ventilator (conventional vs. high-frequency) is able to improve the specific lung pathophysiology being treated is critical to the successful use of the device.

For optimal outcomes, neonates require a combined approach of the bedside nurse, respiratory therapist, and physician or neonatal nurse practitioner. It is critical to understand what is expected to happen to a blood gas when a ventilator adjustment is made. If the expected result does not occur, then it is imperative to assess why (eg, the lung may be overinflated; increasing tidal volume [VT] to improve ventilation will only worsen the problem). There is no place for being a “dial twiddler” (making adjustments without considering the problem being treated) when caring for these vulnerable patients.

Most conventional ventilators are equipped with graphics that enable the user to understand how the lung is responding to treatment. Using airway graphics will significantly improve ventilator management of critically ill patients. A common mistake is to determine initial ventilator settings without considering the pathophysiology of the lung disease being treated. The various ventilator settings will be discussed for both conventional ventilation (CV) and high-frequency ventilation (HFV) devices.
CONVENTIONAL VENTILATION

Today’s conventional ventilators are able to deliver a wide range of Vts accurately. Ventilators that measure Vt at the endotracheal tube (ETT) connection more accurately predict the volume being delivered to the patient’s lungs. Previously, most strategies for ventilation of newborns centered around pressure-limited ventilation. The understanding that lung injury is related to overdistending (volutrauma) has influenced a change from pressure-limited to volume-targeted strategies. There are limitations to the set volume being delivered to the patient. These include inaccuracy of the flow sensor measuring Vt, air leaks around the ETT, variability in the patient’s effort from breath to breath, and inadequate inspiratory time to reach the appropriate Vt. The only patients who will have a constant volume set by the operator are those who are paralyzed or heavily sedated, those who make little or no significant respiratory effort, and those who have no significant air leak around the ETT.

Only the most typical modes will be discussed here, with an emphasis on how to adjust their parameters. The most common mode of CV support is synchronized intermittent mandatory ventilation (SIMV) with volume guarantee (VG). In this mode, a set number of breaths are delivered per minute. They will be synchronized with the patient’s breath. If the patient breathes at a faster rate, the higher number of breaths will not be fully supported, but because pressure support (PS) is generally used, these breaths will be supported with the set PS valve. Positive end-expiratory pressure (PEEP) is set to avoid reaching the closing pressure of the lung. Maximal peak inspiratory pressure (PIP) is set. Inspiratory time (Ti) is usually set at 0.3–0.35 seconds.

The other common mode is assist control (AC) with VG. This mode is similar to SIMV except that the set rate is the minimum rate that will occur if the patient is apneic. All patient-initiated breaths will be completely supported. PIP and Ti are set as with SIMV.

Pressure control ventilation should be used if a large air leak around the ETT is present. PIP is set using graphics to provide adequate lung inflation. PEEP is set to avoid low lung volume at end-expiration. Ti is set at 0.3–0.35 sec for most patients. As compliance improves or worsens, volume delivered will increase or decrease, respectively. This mode requires more frequent assessment and use of graphics to avoid over- and under-inflation of the lung.

The neonate’s lung is very different from that of other patients with diffuse alveolar disease (poor lung compliance). This is because the distensibility of the airways results in an increased dead-space-to-tidal-volume ratio, which prevents a significant volume of gas from reaching the O₂/CO₂ exchange area of the lung. The large open areas are conducting airways, not overdistended saccules (Figure 1).

Figure 1. Preterm baboon with severe Respiratory Distress Syndrome
Large dilated areas are conducting airways.

**Figure 2** demonstrates that, even in Respiratory Distress Syndrome which is considered to be homogeneous, areas of atelectasis and partial inflation are present. This setup increases the chance for lung injury. During CV the more normally inflated area will need to be over inflated (volumtrauma) in order to allow inflation of the atelactatic area. This is due to the compliance of the more inflated area that must be reduced (by over inflation) to be less compliant than that of the atelectatic area in order for volume to be diverted to the atelelactic area to inflate it.

**Figure 2.** Preterm baboon with Respiratory Distress Syndrome showing dense areas (atelectasis) and partially open areas.

The key to protecting the neonate’s lung is to ensure, if possible, that it is maintained at an optimal lung volume. A common mistake is believing that smaller lung volumes are lung protective even though they create atelectasis. Atelectotrauma is as injurious to the lung as volutrauma (**Figure 3**).[10-15]

**Figure 3.** Inflation-deflation loop demonstrating areas that will result in volutrauma and atelectotrauma.
The surfactant-deficient preterm lung is managed by a Vt of 4–6 mL/kg and a rate of 40–50 with a Ti of 0.35 sec. These patients are generally given surfactant to improve their compliance and enable them to achieve optimal lung volume. They typically do well and are able to be transitioned within hours or days to a noninvasive (or less invasive) form of respiratory support.

A small group of these infants will not improve with surfactant. To achieve adequate lung expansion, ventilator adjustments are required. Prolonging Ti to 0.4–0.5 seconds will assist in recruiting poorly inflated areas of the lung. Because these lungs are less stable, a higher level of PEEP is also required. The use of graphics is extremely beneficial for these patients because it helps assess the appropriateness of Vt's and end-expiratory pressure.

HIGH-FREQUENCY VENTILATION

Appropriate initial settings using the high-frequency oscillator (HFOV) depend primarily on the pathophysiology of the lung disease being treated and the patient’s birth weight. Clinicians must keep in mind that these are likely to change over time as the pathophysiology of the lung disease changes. Understanding what effect the various ventilator settings have on the lung of the patient with a specific lung pathophysiology will enable the clinician to provide optimal care.

VENTILATOR PARAMETERS

Mean airway pressure (MAP) is used to keep the lung at optimal lung volume. Its main effect is on oxygenation. However, if it is too low, leading to low lung volume (atelectasis), Paco₂ will be adversely affected, although it will improve when appropriate adjustments are made.

Persistent pulmonary hypertension of the newborn (PPHN) frequently affects patients with severe pulmonary dysfunction. Therefore, increasing MAP to improve oxygenation is helpful if the lung is not adequately inflated, but inappropriate if the lung is adequately inflated and the Pao₂ is low due to PPHN. Overdistending the lung will increase pulmonary hypertension.
Amplitude used to ventilate the patient has little effect on PAO$_2$ except when MAP is too low. In that case, increasing amplitude will increase lung volume but is less lung protective. Amplitude increases peak-to-trough pressure in the airway, helping to open up atelectatic areas. However, if amplitude is three times MAP or greater, the clinician should reassess both MAP and frequency.

Increasing frequency decreases Vt and increases PACO$_2$. Faster frequencies can increase the risk of air trapping, which will increase PACO$_2$ and potentially decrease PAO$_2$. Because decreasing frequency at the same amplitude setting increases Vt, this may increase peak-to-trough pressure in the airway and in the distal lung.

Ventilation during HFV is approximately equal to frequency times Vt squared. During CV, it is equal to frequency times alveolar volume (Vt minus dead space volume).

**HIGH-FREQUENCY JET VENTILATION**

Exhalation is passive, which is why rates used are generally lower. Air trapping may occur at a lower rate than with HFOV. Ti is fixed at 0.02 seconds, and may be increased to 0.03–0.035 seconds for near-/full-term neonates requiring larger volumes. Unlike HFOV, decreasing the rate will generally increase PACO$_2$ due to the fixed Ti. Amplitude is used to provide Vt. PEEP is set using the attached conventional ventilator. Increasing PEEP improves lung inflation by increasing MAP.

Larger-volume conventional breaths can be provided with the attached conventional ventilator. These breaths may be helpful to recruit atelectatic areas, especially in nonhomogenous lung disease. Using more breaths rather than increasing MAP is less lung protective.

**VOLUME DIFFUSIVE RESPIRATOR-4/SINUSOIDAL BRONCHOTRON**

In the Volume Diffusive Respirator-4 (VDR-4)/Sinusoidal Bronchotron (Percussionaire), exhalation is not completely passive since there is some facilitation of exhalation. These devices are completely pneumatic. Changing one parameter will affect other parameters. Delivery is through a phasitron. Ti is adjustable but changes when the rate is changed. Amplitude is adjusted for Vt and will affect MAP. Rates used are somewhat less than those used with HFOV.

Sinusoidal breaths may be used to open atelectatic areas or help remove secretions or meconium. The high-frequency pulsation continues during this breath. These breaths must be carefully regulated as large volumes can be delivered and can result in volutrauma.

**CLINICAL MANAGEMENT OF SPECIFIC PULMONARY PATHOPHYSIOLOGY**

Figure 4 depicts a 650-gram infant with severe diffuse alveolar disease. Basic pathophysiology is poor lung compliance resulting in diffuse atelectasis, protein leak into saccular air space, susceptibility to oxidative injury, and significant difficulty in maintaining optimal lung volume. In our center HFOV is used for initial support in the majority of these patients. 16-18

*Figure 4.* 650-g infant with severe diffuse alveolar disease
MAP should be started at 1–2 cm H_2O greater than for CV. The rate should be 600-900. For patients who do not respond to surfactant, 600 should be used because these patients frequently have pneumonia with airway disease, which increases the risk of air trapping at higher rates. Amplitude should be adequate for a small amount of chest wall movement.

If the patient is not on CV at birth, MAP should be started at 2–3 cm H_2O greater than CPAP, typically 8–10 cm H_2O. MAP should be increased by 1 cm H_2O every 2–5 minutes until saturation reaches 90%, at which point it should be held there. If saturation does not continue to rise, then MAP should be increased by 1–2 cm H_2O more. Once F_{IO_2} is less than 0.7, to avoid lung over expansion the MAP should be slowly reduced as long as F_{IO_2} can also continue to be reduced. The average MAP for patients treated with surfactant who respond is 8–11 cm H_2O. The average MAP for patients who do not respond is 14–20 cm H_2O.

For high-frequency jet ventilation (HFJV), MAPs are somewhat lower, by 1–4 cm H_2O, and rates are 360–480. Conventional breaths should not be needed if MAP is adequate.

For the VDR-4 ventilator, MAP is similar to that of HFOV. Sinusoidal breaths are generally not needed if MAP is adequate. Rate is 360–480.

**CONVENTIONAL VENTILATION**

In general, a volume-targeted mode is used. Typically we use SIMV with VG plus PS or AC plus PS\(^{18}\) for patients who have responded to surfactant. Typically a Vt of 4–5 mL/kg is adequate, with a rate of 40–50, a Ti of 0.3–0.35 sec, and a PEEP of 4–5 cm H_2O. For patients such as the one shown in Figure 1, a longer Ti (0.4–0.45 sec) is needed initially to recruit atelectatic areas, with a Vt of 5–7 mL/kg and a PEEP of 6–8 cm H_2O.

Once well recruited, the Ti should be decreased. Because this lung may be less stable due to inadequate surfactant production or inactivation from infection, PEEP will likely need to stay at 6–8 cm H_2O. Graphics can assist in determining how to adjust rate, PEEP, and Vt.

**LATE PRETERM AND TERM INFANT WITH DIFFUSE ALVEOLAR DISEASE**
Figure 5 depicts a 3,000-g 36-week gestational age boy with severe diffuse alveolar disease. HFOV settings are: MAP 2–4 cm H$_2$O > CV, rate 480-600. Lower rates are chosen because of the likelihood of infection with airway disease that can lead to air trapping. Amplitude should be set to provide visible chest wall movement. Average MAP for patients who have some response to surfactant is 12–18 cm H$_2$O; for those who do not respond to surfactant, it is 18–30 cm H$_2$O. All of these patients frequently have PPHN, which will require nitric oxide or other pulmonary vasodilators.

For HFJV, MAP should be 1–2 cm H$_2$O less than HFOV. Ti may need to be increased to provide larger Vt jet breaths. Conventional breaths should be minimal. Larger Vt breaths from the conventional ventilator combined with the jet make it less lung protective.

Conventional breaths are often used to improve ventilation and decrease FIO$_2$. Higher MAP will decrease their need for improving ventilation and decreasing FIO$_2$. These breaths should be kept to the minimum needed. The PIP of the breath should be greater than the jet amplitude in order to pause the jet pulsation.

VDR-4 settings: MAP should be started similar to that for HFOV. In general, frequencies are lower—in the 360-480 range. Amplitude should provide visible chest wall movement. Sinusoidal breaths should be kept at a minimum 1–4. If cardiac output is poor, a lower MAP can be used and will require an increase in frequency of the sinusoidal breaths.

CV settings: Vt should be in the range of 5–7 mL/kg. PEEP should be adjusted from 6–8 cm H$_2$O. For unstable lungs, higher Vt and PEEP will be needed. Ti should be 0.35–0.4 sec. Rate should be 40–50, adjusted for blood gas analysis results. Graphics should be used to ensure that the patient does not derecruit at PEEP level.

Nonhomogenous Lung Disease

Figure 6 depicts a term infant with severe meconium aspiration. Noted are air leaks over distension and atelectasis. The pathophysiology of meconium aspiration with air trapping includes areas of atelectasis and overdistension due to meconium in the airway with a ball valve effect. Also, there may be inactivation of surfactant. Pulmonary hypertension is an additional component of this disorder.

Figure 6. Term infant with severe meconium aspiration with air leak
HFOV settings: MAP should be started at the same level as for CV. Rate should be 300-480, and amplitude should be set to provide good chest wall bounce. The key is low frequency and increased amplitude, which will open airways and atelectatic areas and assist in removal of meconium. MAP may need to be increased to improve oxygenation.

PPHN is likely to be part of the pathophysiology of nonhomogenous lung disease. Cardiac echocardiography should be performed. Nitric oxide and other pulmonary vasodilators are frequently needed. Surfactant is frequently beneficial. If the patient has significant PPHN, nitric oxide may help prevent it from severely increasing when surfactant is given, because surfactant will temporarily decrease Pao$_2$ and increase Paco$_2$.[25-27]

HFJV settings: MAP should be started at the same level as for CV. Rate should be in the range of 240-420. Ti may need to be increased to provide larger volumes. Increasing amplitude may assist in removing secretions.

VDR-4 settings: Rate should be 300-420. MAP should be the same as for CV. Amplitude should be set to provide good chest bounce. If air leak is minimal or not active, sinusoidal breaths may be added. These will help open up atelectatic areas. The VDR-4 appears to work well for these patients.

SIMV with VG (CV) settings: Rate should be 30–40 because faster rates are likely to result in air trapping. Vt should be 5–6mL/kg, and PEEP 5–7 cm H$_2$O. Graphics should be used to assist in adjusting the ventilator. Frequent suctioning will help clear secretions.

NONHOMOGENEOUS LUNG DISEASE WITH LOW LUNG VOLUMES

Figure 7 shows a term newborn with history of meconium in his trachea at birth, but poorly expanded. Because these patients have a predominantly low lung volume, higher MAP is needed. However, lower frequencies should be used because there may be meconium in the airways, leading to air trapping.

Figure 7. Term infant with meconium aspiration pneumonia without air leak or air trapping
HFOV settings: MAP should be 2–5 cm H₂O greater than CV. Rate should be 360-540, and is generally 420-480. Amplitude should provide good chest wall bounce. Surfactant may be used if MAP is required to be in the mid- to upper 20s cm H₂O or if the patient remains poorly oxygenated.

HFJV settings: MAP should be increased to 2–4 cm H₂O above the mean for CV. Rate should be 300-420. PIP/amplitude should be adjusted for chest wall bounce.

VDR-4 settings: MAP should be 2–5 cm H₂O greater than CV. Rate should be 300-480, and amplitude set for good chest wall bounce. Sinusoidal breaths can be used at 1–5/min. Large chest rise with these breaths should be avoided because this can lead to volutrauma.

CV settings: Vt should be 5–6 mL/kg. PEEP should be in the range of 6–9 cm H₂O. Rate should be 30–40 to avoid air trapping. Graphics should be used to avoid derecruitment on exhalation and overdistension on inspiration.

**UNIFORM PULMONARY HYPOPLASIA**

Patients with uniform pulmonary hypoplasia have small lungs due to either prolonged rupture of membranes or renal problems with low amniotic fluid or giant omphalocele (Figure 8) or hydrops with large pleural effusions (Figure 9). These patients frequently have surfactant problems because they are premature or as part of hypoplasia.

*Figure 8.* Patient with pulmonary hypoplasia due to maternal rupture of membranes at 15 weeks estimated gestational age

*Figure 9.* Patient with uniform pulmonary hypoplasia due to hydrops
PPHN is a common additional problem for patients with uniform pulmonary hypoplasia. If PPHN is present, nitric oxide or another vasodilator should be used. Adequate lung inflation is based on how clear the lung fluids are radiographically. Lung expansion may need to be only 6 or 7 ribs. Trying to inflate the lung further will lead to lung injury. I typically use HFOV for these patients.

HFOV settings: MAP should be the same as that used for CV. It should be advanced 1 cm H$_2$O every 2–3 minutes until preductal saturation increases to above 90%. Rate should be 600-900, depending on gestation. Amplitude should provide minimal chest wall movement.

HFJV settings: MAP should be the same as for CV, as with HFOV. It should be advanced 1 cm H$_2$O every 2–3 minutes until preductal saturation >90%. Rate should be 360-480. No conventional breaths should be added. PIP/amplitude should provide minimal chest wall movement.

VDR-4 settings: MAP should be the same as that used for CV. It should be increased 1 cm H$_2$O every 2–3 minutes until preductal saturation >90%. Rate should be 300-480. Amplitude should be set for small chest wall bounce. Sinusoidal breaths should not be used.

SIMV with VG (CV) settings: Vt should be 4–5mL/kg, with PEEP 6–8 cm H$_2$O, and rate 40. Graphics should be used to prevent derecruitment and avoid overexpansion with Vt. If required PIP exceeds 26–28 cm H$_2$O, the clinician should consider choosing a high-frequency mode.

NONUNIFORM PULMONARY HYPOPLASIA

Predominately diaphragmatic hernia can also be seen with unilateral paralyzed diaphragm or cystic adenomatoid malformation. The pathophysiology consists of one relatively normal lung and one hypoplastic lung. There is frequently associated pulmonary hypertension. Gentle ventilation is used to minimize injury to the hypoplastic lung.

HFOV settings: Rate is generally 480-600 if the contralateral lung is essentially normal. MAP should be 10–14 cm H$_2$O. In the late preterm/full-term infant, MAP should not be increased above 14 cm H$_2$O without a chest radiograph demonstrating poor expansion of the normal lung. Amplitude should be set to provide small to moderate chest wall bounce. Paco$_2$ goal is 45–55 mm Hg. The non-hypoplastic lung needs to be expanded to 10–10.5 ribs (Figures 10 and 11).
Figure 10. Radiograph of a patient with a left diaphragmatic hernia with inadequate right lung expansion

Figure 11. Radiograph of same patient with adequate right lung expansion

Keeping the patient at 9 ribs inflation results in needing 100% oxygen and ultimately extracorporeal membrane oxygenation. A MAP that creates optimal lung volume will result in a lung that is at 10–10.5 ribs inflated but requires much less \( F_{\text{IO}_2} \) and is capable of being steadily weaned.

HFJV settings: Rate should be 300-420. MAP should be the same as for HFOV. PIP/amplitude should be set for \( \text{Paco}_2 \) 45–55 mm Hg, and PEEP 4–6 cm H\(_2\)O. Conventional breaths are generally not needed. If cardiac output is poor, 2–6 breaths may be added with decreasing MAP by 1 cm H\(_2\)O.

CV settings: Vt should be 4–5 mL/kg, rate 40, PEEP 4–6 cm H\(_2\)O to prevent derecruitment. Ti should be 0.3–0.35 sec, and max PIP < 25 cm H\(_2\)O. Again, graphics will assist in making ventilator adjustments.

PPHN is very common in these patients. Nitric oxide or other vasodilators can be beneficial. However, if the left ventricle is not functioning well, nitric oxide should not be used until it is treated and output improved.

GROSS AIR LEAK – PRETERM INFANTS

Figure 12 shows a preterm infant with a left pneumothorax.
Air leak premature infant

**Figure 12.**

HFOV settings: MAP should be the same as or 1 cm H\(_2\)O greater than CV. Rate should be 600-900. Amplitude should provide minimal chest wall movement. Adjust for Paco\(_2\) 50–60 mm Hg as long as pH is 7.25 or greater.

HFJV settings: MAP should be 1 cm H\(_2\)O less than CV. Rate should be 420-600. PEEP should be set as needed for MAP. Amplitude/PIP, adjust for Paco\(_2\) 50–60 mm Hg as long as pH is 7.25 or greater. No conventional breaths should be added.

VDR-4/Sinusoidal Bronchotron settings: MAP should be the same as or 1 cm H\(_2\)O less than CV. Rate should be 420-600, with amplitude to provide minimal chest wall movement. No sinusoidal breaths should be added.

CV settings: For SIMV and VG, rate should be 40–50, Ti 0.3–0.35 sec, Vt 4 mL/kg, and PEEP 4–5cm H\(_2\)O. The goal of Paco\(_2\) is 50–60mm Hg, pH 7.25 or greater. Persistent air leak is related mostly to MAP but also to amplitude, with HFV and more to Vt with CV and suggests a need to change to HFV mode.

**PULMONARY INTERSTITIAL EMPHYSEMA**

Air leak with pulmonary interstitial emphysema (PIE) occurs typically in very-low-birth-weight preterm infants. The use of antenatal steroids and surfactant have significantly reduced its frequency. The leak occurs in a distal airway rather than the saccule, which explains the severity. The goal is to minimize leak and allow the PIE to resolve. The strategy is determined based on the initial severity. **Figure 13** shows an infant with less severe PIE, predominantly in the left lung. As such, putting that side down will help. **Figure 14** shows an infant with more severe PIE. In this patient, compression of airways with PIE leads to an increased risk of air trapping, which is why the strategy is different. Most PIE patients are treated best with HFV mode.

**Figure 13.** Pulmonary interstitial emphysema, less severe
HFOV settings for less severe PIE (Figure 13): MAP should be 1 cm H$_2$O less than CV. Rate should be 600-900. Amplitude should provide minimal chest wall movement.

HFOV settings for more severe PIE (Figure 14): MAP should be 1 cm H$_2$O above CV to help keep the airway open. Rate should be 420-600 because of the increased risk of air trapping. Amplitude should provide minimal chest wall movement.

HFJV settings for less severe PIE (Figure 13): MAP should be 2 cm H$_2$O less than that used for CV. Rate should be 420-480. PIP/amplitude should provide minimal chest wall movement. Paco$_2$ should be kept at 50–60 mm Hg. No conventional breaths should be added.

HFJV settings for more severe PIE (Figure 14): MAP should be the same or 1 cm H$_2$O above CV. Rate should be 300-420. PIP/amplitude should keep Paco$_2$ at 50–60 mm Hg.

VDR-4 is generally not used for PIE.

CV settings (SIMV or AC mode) for less severe PIE (Figure 13): Vt 3–4 mL/kg, rate 50–60, Ti 0.3–0.35 sec, and PEEP 4–5 cm H$_2$O.

CV settings (SIMV or AC mode) for more severe PIE (Figure 14): Vt 3 mL/kg, rate 50–60, Ti 0.3–0.35 sec, PEEP 5–7cm H$_2$O to help keep airways open.

**LATE PRETERM AND TERM INFANTS**
Diffuse alveolar disease and infection are common causes of air leak in late preterm and term infants (Figure 15). Because of the potential for air trapping, somewhat lower frequencies are recommended for HFV in these patients. Their pathophysiology is a combination of diffuse alveolar disease (requiring increased PEEP and MAP) and air leak, which requires lower MAP and PIP/amplitude. Once the lung is recruited with appropriate ventilator settings which allows the FiO₂ to be decreased then the MAP should be weaned to decrease air leak.31

Figure 15. Gross air leak with poor inflation

HFOV settings: MAP should be 2–3 cm H₂O greater than CV. Rate should be 480-600. Amplitude should provide visible chest wall movement. Once well oxygenated, MAP should be decreased.

HFJV settings: MAP should be 1–2 cm H₂O above CV. Rate should be 300-420. PIP/amplitude should provide visible chest wall movement. Only 1 or 2 conventional breaths should be added.

VDR-4 settings: MAP should be 1–2 cm H₂O above CV. Rate should be 360-480. Amplitude should provide visible chest wall movement. Only 0–2 sinusoidal breaths should be added.

CV settings (SIMV or AC mode with VG): Vt should be 4–6 mL/kg, rate 40, Ti 0.35–0.4 sec, PEEP 5–7 cm H₂O. Graphics should be used to assess where the pressure volume loop is. It should be in the mid-portion. If air leak persists, changing to HFV mode should be considered.

GROSS AIR LEAK WITH ADEQUATE INFLATION

The pathophysiology of a gross air leak with adequate inflation is a normal lung requiring low MAP, PEEP, and PIP/amplitude to reduce air leak. (Figure 16).

Figure 16. Gross air leak with adequate inflation
HFOV settings: MAP should be the same as or 1 cm H$_2$O lower than CV. Rate should be 480-600. Amplitude should provide visible chest wall movement. If air leak persists, decrease MAP and/or amplitude.

HFJV settings: MAP should be 1–2 cm H$_2$O lower than CV. Ti should be 0.02 sec. Amplitude for Paco$_2$ should be 45–55 mm Hg. Rate 360-480. No conventional breaths should be added. If air leak persists, decrease MAP and/or amplitude, if needed.

VDR-4 settings: MAP should be 1–2 cm H$_2$O lower than CV. Amplitude should provide visual chest wall movement. Rate should be 300-420. If air leak persists, decrease MAP and/or amplitude if needed.

CV settings (SIMV with VG): Rate should be 30–40. Ti should be 0.3 sec. Vt should be 4 mL/kg.

**WEANING STRATEGIES**

Weaning from CV depends on the mode being used. For SIMV with VG with PS, the rate will decrease the number of completely supported breaths. If minute ventilation remains the same, the patient is providing additional support. However, the degree of PS will assist every breath and may provide adequate support for the patient even if the patient will not tolerate extubation. In general, PS will also need to be reduced. Some ventilators have tube compensation that allows the patient to be placed on endotracheal CPAP since enough support is provided with each breath to overcome the tube dead space and the pressure required to clear it.

For AC and VG, the volume needs to be reduced as all breaths are supported. PEEP may need to be increased to keep the MAP higher. The calculated minute volume is followed because it should remain close to the same if the patient is tolerating a decrease in ventilator support by increasing their own effort. This is also demonstrated by the PIP required to reach the set Vt is decreased to low levels typically 8-12 H$_2$O

In general, patients who have been on assisted ventilation for more than 7–10 days will do better if given 3–4 doses of dexamethasone, 0.2–0.3 mg/kg every 12 hours, starting at least 12 hours before extubation.

Patients with poorly compliant lungs will do best if they are transferred to CPAP. Those who have increased Paco$_2$ or apnea will do best on nasal intermittent positive pressure ventilation, high-frequency nasal ventilation, or nasal neutrally adjusted ventilator assist. When using humidified high-flow nasal cannula, it is preferred to start at 5–6 L because allowing the lung to derecruit will likely result in failure of the
extubation trial.

**GENERAL PRINCIPLES FOR WEANING HFOV**

**MAP**

If > 20 cm H\textsubscript{2}O, decrease by 2 cm H\textsubscript{2}O.
If 10–20 cm H\textsubscript{2}O, decrease by 1 cm H\textsubscript{2}O.
If <10 cm H\textsubscript{2}O, decrease by 0.5 cm H\textsubscript{2}O.

**Amplitude**

If Paco\textsubscript{2} <35 mm Hg, decrease by 2–4 mm Hg.
If Paco\textsubscript{2} 35–45 mm Hg, decrease by 1–3 mm Hg.
If Paco\textsubscript{2} 45–50 mm Hg, decrease by 1–2 mm Hg.

**Rate**

If lung is overdistended but patchy, decrease by 60–120.

**Extubation Settings**

- >2 kg
  - MAP: 11–13.5 cm H\textsubscript{2}O
  - Amplitude: 15–22
  - Rate: 360–600
- 1–2 kg
  - MAP: 9–11 cm H\textsubscript{2}O
  - Amplitude: 12–20
  - Rate: 420–720
- 1 kg
  - MAP: 6–10 cm H\textsubscript{2}O
  - Amplitude: 10–16
  - Rate: >600

**WEANING FROM HIGH-FREQUENCY OSCILLATORY VENTILATION**

Preterm infants with diffuse alveolar disease are weaned differently depending on whether they respond to surfactant or do not respond to it.

For surfactant responders: MAP should be 8–11 cm H\textsubscript{2}O. It should be weaned once the patient is on 30% oxygen. If MAP is >10 cm H\textsubscript{2}O, it should be weaned by 1 cm H\textsubscript{2}O. If MAP is <10, it should be weaned by 0.5 cm H\textsubscript{2}O. If Paco\textsubscript{2} <35 mm Hg, amplitude should be decreased by 2–4 mm Hg. If Paco\textsubscript{2} is 35–40 mm Hg, amplitude should be decreased by 1–3 mm Hg. If Paco\textsubscript{2} is 45–50 mm Hg, amplitude should be decreased by 1–2 mm Hg.

For surfactant nonresponders: MAP should be 11–15 cm H\textsubscript{2}O. Once F\textsubscript{io2} is less than 0.6–0.7, MAP can be decreased by 1–3 cm H\textsubscript{2}O. If MAP > 20 cm H\textsubscript{2}O, it can be decreased by 2 cm H\textsubscript{2}O. If MAP is 10–20 cm H\textsubscript{2}O, it can be decreased by 1 cm H\textsubscript{2}O.

**DIFFUSE ALVEOLAR DISEASE IN LATE PRETERM AND TERM INFANTS**
Late preterm and term infants are those 34 weeks or older. For those with diffuse alveolar disease, once $FIO_2$ is <0.7, MAP should be decreased. If MAP > 30 cm H$_2$O, it can be weaned by 2 cm H$_2$O every 15 minutes as long as $O_2$ saturation does not decrease. The goal is to decrease MAP by 6–8 cm H$_2$O. If MAP is 20–30 cm H$_2$O, MAP should be decreased by 2 cm H$_2$O. The goal is to decrease MAP by 4–6 cm H$_2$O. If MAP is 15–20 cm H$_2$O, MAP should be decreased by 1 every 15–30 minutes. The goal is to decrease MAP by 2–4 cm H$_2$O.

For late preterm and term infants, the overall goal during the first several hours is to reduce $FIO_2$ to less than 0.7; for very-low- and extremely-low-birth-weight infants, it should be reduced to less than 0.5. Overdistension and atelectasis should be avoided, and extubation should be achieved as early as possible, thus minimizing not only pulmonary injury but also injury to other organs.

**KEY POINTS**

- It is important to understand how the ventilator being used works for the pathophysiology being treated.
- It is important to be cognizant of how ventilator adjustments affect blood gases.
- If using conventional ventilation, graphics should be used.
- Pulmonary pathophysiology changes over time. What worked yesterday might not work today.
- Mechanically ventilated patients should not be on autopilot. They should be frequently reassessed.
- Pulmonary hypertension is a frequent problem with mechanically ventilated patients. It should be looked for and treated.
- Oxygen exposure should be minimized. $Pao_2$s above 80 mm Hg are not needed and may add to oxidative injury of the lung and other organs.
- The patient should be extubated as early as possible, using less invasive techniques.
- Frequent physical assessments are required.

**CASE STUDY 1**

A 2.2-kg 33-week estimated gestational age girl has a prenatally diagnosed left diaphragmatic hernia. Apgar scores were 6 at 1 minute and 8 at 5 minutes. She was intubated in her first minute of life and an Andersen orogastric tube was placed. She was ventilated with a HFOV with a MAP of 14 cm H$_2$O, frequency of 8 Hz, and amplitude of 32 on 100% $O_2$. Blood gas analysis showed $Pao_2$ of 124 mm Hg and $Paco_2$ of 42 mm Hg (**Figure 17**).

**Figure 17.** 2.2-kg 33-week girl with prenatally diagnosed left diaphragmatic hernia
MAP was decreased to 13 cm H$_2$O and amplitude to 31. Blood gas analysis on 100% O$_2$ showed Pao$_2$ 116 mm Hg and Paco$_2$ 38 mm Hg. Fio$_2$ decreased to 0.84, and amplitude decreased to 29. Blood gas analysis showed Pao$_2$ 115 mm Hg and Paco$_2$ 43 mm Hg. MAP was decreased to 12.5 cm H$_2$O, then 12 cm H$_2$O, with an amplitude of 31. One hour later, Pao$_2$ was 68 mm Hg and Paco$_2$ 43 mm Hg. Chest radiograph is shown in Figure 18. MAP was increased to 13–13.5 cm H$_2$O and 14 cm H$_2$O over the next 15 minutes. A follow-up chest radiograph is shown in Figure 19. At this time, the patient was on 100% oxygen with a Pao$_2$ of 51 mm Hg and Paco$_2$ of 46 mm Hg. MAP was increased to 15.5 cm H$_2$O (Figure 20). Over the next 12 hours, the Fio$_2$ was able to be decreased to 0.74 with a Pao$_2$ of 96 mm Hg and a Paco$_2$ of 44 mm Hg, and the MAP decreased to 13.5 cm H$_2$O.

*Figure 18.* Chest radiograph

*Figure 19.* Follow-up chest radiograph
Once a patient’s lung is allowed to derecruit, the MAP will need to be increased 2–4 cm H$_2$O above the pressure that resulted in the derecruitment to get the lung adequately expanded again. The MAP can then be reduced to 1.5-2 cm H$_2$O above the derecruitment pressure.

**Case Study 2**

A 26-week-old gestational age boy continues to require assisted ventilation at 14 days of age. Ventilator settings on HFOV are: MAP 10.5 cm H$_2$O, frequency 10 Hz, amplitude 14, F$_{\text{IO}_2}$ 0.35. Blood gas analysis reveals pH 7.32, Pao$_2$ 62 mm Hg, and Paco$_2$ 48 mm Hg. Based on the radiograph in Figure 21, MAP is decreased to 9.5 cm H$_2$O. One hour later, ventilator settings are: MAP 9.5 cm H$_2$O, frequency 10 Hz, amplitude 18, and F$_{\text{IO}_2}$ 0.5. Blood gas analysis reveals pH 7.25, Pao$_2$ 68 mm Hg, and Paco$_2$ 52 (Figure 22). MAP is increased back to 10.5 cm H$_2$O, frequency decreased to 8 Hz, amplitude to 16, and F$_{\text{IO}_2}$ to 0.3. Blood gas analysis reveals pH 7.34, Pao$_2$ 70 mm Hg, and Paco$_2$ 46 mm Hg. Decreasing the frequency results in less air
trapping with improved blood gas and a lower FIO₂.

**Figure 21.** 26-week-old gestational age boy radiograph

**Figure 22.** Blood gas analysis

Comparing the radiographs in Figures 23 and 24, Figure 23 is overinflated because of too high a MAP with very clear lung fields. Figure 24 is overinflated because of air trapping from too fast a frequency. Airway disease results in air trapping if the frequency is too fast. Note that the lung fields are hazy, not clear.

**Figure 23.** Radiograph showing overinflation due to high MAP with very clear lung fields

**Figure 24.** Radiograph showing overinflation due to air trapping from too fast a frequency
Case Study 3

A 3.7-kg full-term boy was born via spontaneous vaginal delivery with Apgar scores of 7 at 1 minute and 8 at 5 minutes. The mother is known to be infected with Group B streptococcus. The boy developed respiratory distress within 10 minutes of birth. Oxygen saturation was 75% on room air, and 88% on 100% O₂ (Figure 25). He was intubated and placed on SIMV with VG with PS. Vt was set at 6 mL/kg, PEEP at 6 cm H₂O, rate at 40, MAP at 13 cm H₂O, and FIO₂ 1.0. Arterial blood gas analysis showed pH 7.2, Paco₂ 65 mm Hg, Pao₂ 40 mm Hg, preductal saturation 90%, and postductal saturation 80%. Cardiac echocardiography was consistent with systemic right ventricle pressures. Right and left ventricle function were normal.

Figure 25. 3.7-kg full-term boy

Nitric oxide (NO) was started at 20 ppm. Vt was increased to 7 mL/kg, PEEP to 8 cm H₂O, and MAP to 15 cm H₂O. Blood gas analysis on 100% O₂ showed pH 7.24, Paco₂ 62 mm Hg, Pao₂ 44 mm Hg, preductal saturation 90%, and postductal saturation 82% (Figure 26). Options include increasing nitric oxide to 30 ppm, increasing Vt to 8mL/kg, or beginning HFOV.

Figure 26. Blood gas analysis

Why has the patient not responded to NO? One of the common reasons patients with pulmonary hypertension fail to respond to NO is inadequate lung expansion. In order for NO to work it must get to the aveolus/saccule in order to diffuse to the
vascular bed and cause vasodilation. The patient was started on HFOV MAP of 19, rate 480, amplitude 35, and NO continued at 20. Blood gas 30 minutes later: pH 7.30, PaCO$_2$ 54, PaO$_2$ 56 in FIO$_2$ 1.32 The MAP was increased to 24 and blood gas 15 minutes later was pH 7.38, PaCO$_2$ 48, PaO$_2$ 180 with preductal saturation 99 and postductal saturation 98.

Two hours later the patient was in FIO$_2$ 0.55 with pH 7.35, PaCO$_2$ 46, PaO$_2$ 64. MAP was continued at 24 amplitude 35 and rate 480. Six hours later the patient’s blood pressure decreased from 68/40 52 to 48/30 38. Preductal and postductal saturations decreased from 98 to 92 preductal and 88 postductal ventilator settings were unchanged except FIO$_2$ had increased from 0.55 to 0.8. ABG was pH 7.28, PaCO$_2$ 58, PaO$_2$ 58.

What should be considered? Pneumothorax, cardiac failure, overexpansion or under expansion of the lung (Figure 27). On physical examination, the liver was noted to be 3 cm below the right coastal margin. Based on that physical finding, the MAP would have been reduced, without waiting for a chest radiograph, to 21. FIO$_2$ was reduced to 0.5. Over the next 6 hours the MAP was reduced to 17 and FIO$_2$ to 0.35.

**Figure 27.** Pneumothorax, cardiac failure, overexpansion or under expansion of the lung

---

**REFERENCES**

30. Kinsella JP, Ivy DD, Abman SH. Pulmonary vasodilator therapy in congenital diaphragmatic


Chapter 8

MANAGING VENTILATOR SUPPORT OF NORMAL LUNGS IN ADULT AND PEDIATRIC PATIENTS

Anoopindar Bhalla, MD, Christopher Newth, MD, FRCPC, Paolo Pelosi, MD, Marcelo Gama de Abreu, MD, Gisele Padilha, and Lorenzo Ball, MD

Objectives

- Identify strategies to implement lung-protective ventilation in pediatric and adult patients with normal lungs
- Understand the pathophysiology of ventilator-induced lung injury in healthy lungs
- Recognize the hemodynamic effects of mechanical ventilation
- Understand the normal lung and chest wall developmental changes that occur in pediatric patients

INTRODUCTION

Mechanical ventilation is a necessary measure for about 35% of patients in intensive care units (ICUs) worldwide. Despite improvement over the years, the mortality of these patients remains at approximately 30%.1 The main indication for mechanical ventilation is respiratory failure due to lung function impairment. However, patients with non-injured lungs also often require this intervention, for example, during general anesthesia for surgery and/or in the postoperative period, as well as for neurologic and neuromuscular disorders.

The main goal of mechanical ventilation is to support the respiratory function, as long as the patient is recovering from the underlying cause that prompted its need. As such, mechanical ventilation serves merely as a bridge to maintain adequate gas exchange and/or reduce the work of breathing. Although it is a life-saving intervention, invasive mechanical ventilation carries several potential risks, and can aggravate previous lung injury, mainly in patients with acute respiratory distress syndrome (ARDS). In fact, mechanical ventilation itself can lead to ventilator-induced lung injury (VILI) in patients with no previous lung injury.2 Several mechanisms of VILI have been described, including barotrauma, volutrauma, and energy trauma,3 mediated by the recruitment of neutrophils and the release of inflammatory mediators. However, the ability to manage the ventilatory parameters within certain safe ranges can limit the development of VILI, and even decrease morbidity and mortality. Thereby, gas exchange, as long as it matches the basic metabolic needs, plays a secondary role compared to the minimization of VILI. This paradigm shift toward strategies aimed at protecting lungs from the stress of mechanical ventilation, instead of achieving luxurious oxygenation, has been gaining acceptance worldwide, not only for patients with ARDS, but also for patients without preexisting lung injury.

Children with normal lungs may require invasive mechanical ventilation for a variety
of reasons. A study conducted in 16 U.S. pediatric ICUs showed that 26% of the children were mechanically ventilated for non-pulmonary conditions, including neuromuscular disease, intracranial hypertension, spinal instability, abdominal wounds, and heart failure. Another common population of mechanically ventilated children with relatively normal lungs are those with congenital heart disease. These children are often ventilated in the perioperative period and have unique hemodynamic considerations.

Unfortunately, there is relatively little data in pediatrics to guide appropriate mechanical ventilation in children, and much clinical practice is based on experience and adult evidence. However, it is important to understand the anatomic and physiologic characteristics of children to guide the management of mechanically ventilated children, particularly those with normal lungs. The primary goal of ventilator management in children with normal lungs is to prevent or limit any of the known dangers of invasive mechanical ventilation such as VILI, delirium, and airway trauma. Appropriate airway management, ventilator settings, and monitoring can decrease the risk of harm in this population.

The aim of this chapter is to illustrate the practice of ventilatory support in patients whose lungs are not injured at ICU admission or at the time mechanical ventilation is initiated.

BRIEF ADULT CASE STUDY

A 63-year-old woman who is not obese was admitted to the ICU for a subarachnoid hemorrhage. Her neurologic status suddenly worsened while undergoing computed tomography. Because her Glasgow Coma Scale score was 5/15, she was intubated and mechanically ventilated by the emergency department physician. A chest radiograph showed no major lung alterations. When transferred to the ICU, the patient was ventilated in pressure support mode with peak inspiratory pressure 14 cm H_2O, positive end-expiratory pressure (PEEP) 5 cm H_2O, and FIO_2 0.35. She developed tachypnea (32 breaths/min), with a high tidal volume (VT) of 12 mL/kg predicted body weight (PBW), resulting in hypocapnia (Paco_2 of 22 mm Hg), despite adequate oxygenation (Spo_2 99%). The intensivist tried to decrease the respiratory rate (RR) and VTs, increasing sedation and reducing the inspiratory pressure (Pinsp), but these attempts failed, and tachypnea persisted. The intensivist decided to administer a neuromuscular blocking agent, and switch mechanical ventilation to volume control mode. The ventilator was set to deliver a VT of 7 mL/kg PBW, with PEEP 3 cm H_2O, FIO_2 0.30, and RR 14 cycles/min. Under these settings, Spo_2 remained acceptable (95%) and Paco_2 was in the normal range (38 mm Hg).

BRIEF PEDIATRIC CASE STUDY

A previously healthy three-year-old boy weighing 15 kg was admitted to the ICU after laparotomy for volvulus with necrotic small bowel requiring a 90 cm resection. His initial ventilator settings were pressure control pressure support with peak inspiratory pressure 28 cm H_2O, PEEP 5 cm H_2O, inspiratory time 0.7 sec, RR 24 cycles/min, and FIO_2 0.4. His VTs on these settings were 6 mL/kg. He was on dopamine, 10 µg/kg/min, and epinephrine, 0.04 µg/kg/min. Initial arterial blood gas analysis at ICU admission revealed: pH 7.3, Paco_2 50 mm Hg, and Pao_2 60 mm Hg. During the next
several hours he required fluid resuscitation for hypotension. His oxygenation saturation was 92% with frequent desaturations down to 85%, although FIO\(_2\) had been increased to 0.8. Subsequent arterial blood gas analysis revealed: pH 7.2, Paco\(_2\) 70 mm Hg, and Pao\(_2\) 50 mm Hg. Vts were now 4 mL/kg. A chest radiograph demonstrated poor expansion with reduced lung volumes. The intensivist recognized that the patient might benefit from additional PEEP to counterbalance the increased pleural pressure due to his abdominal distension. Accordingly, PEEP was increased stepwise until the best compliance was achieved, at 12 cm H\(_2\)O. Within minutes of increasing the PEEP, his blood pressures started to decline, and an additional fluid bolus was provided. The intensivist decided to reduce the PEEP to 10 cm H\(_2\)O, and the blood pressures increased again. During the following several hours, oxygen saturations increased to 96% and FIO\(_2\) was weaned back to 0.4.

**LESSONS FROM MECHANICAL VENTILATION IN ARDS**

ARDS occurs in more than 10% of the patients admitted to the ICU. Patients who survive ARDS often develop long-term sequelae, such as neuropsychological impairment, pulmonary dysfunction, and consequently decreased quality of life. Historically, the traditional mechanical ventilation strategy comprised the use of high Vts without a clear understanding of its deleterious effects. Higher Vts were preferred in order to avoid hypoxemia and atelectasis, which are commonly associated with mechanical ventilation using lower Vts. Accordingly, the use of Vts around 12–15 mL/kg was a common practice in the 1990s. However, in a landmark trial by the ARDS Network, ventilation with low Vt ranging from 4 to 8 mL/kg (mean of approximately 6 mL/kg) PBW was shown to improve survival in patients with ARDS, when compared with ventilation using 12 mL/kg PBW. Currently, the combination of low Vt of 6–8 mL/kg PBW with moderate to high levels of PEEP, usually without accompanying recruitment maneuvers, has become common practice in the ventilatory management of ARDS; this is referred to as lung-protective ventilation. Lung-protective ventilation has significantly reduced morbidity and mortality among patients with ARDS, becoming widely accepted as the safest and most effective strategy toward lung protection in these patients.

**PATHOGENESIS OF VENTILATOR-INDUCED LUNG INJURY**

VILI can occur in mechanically ventilated patients for any reason. The phenomenon of collapse of lung units during exhalation followed by re-opening during inhalation, cyclic alveoli overdistension during inhalation, and exposure to high fractional oxygen levels are all associated with VILI. VILI is a process characterized by inflammatory pulmonary infiltrates, increased vascular permeability, and pulmonary edema, which is associated with multisystem organ failure and increased mortality. Higher Vt is an independent risk factor for the development of ARDS. While there are no clinical studies concerning the risk of developing VILI in mechanically ventilated children with normal lungs, there is evidence from animal studies that children may be at lower risk for VILI than adults.

Another important consideration in patients with normal lungs who are mechanically ventilated is that they have the best potential for weaning from mechanical ventilation if respiratory muscle atrophy is limited. Diaphragm atrophy has been shown to occur as early as the first day in adults who have been fully supported by mechanical
ventilation and can be further compounded in those who are under neuromuscular blockade. Ventilation through pressure support, where the patient triggers a breath and the support provided is generally less than through controlled breaths, may be allowed, as it can decrease the amount of ventilator-induced diaphragm atrophy. In the past, many clinicians believed that children should never be ventilated with low pressures because of the high resistance through a small-diameter endotracheal tube; ie, it is as if they are breathing through a straw. This has been shown not to hold true, since the resistance through a small-diameter endotracheal tube is similar to the resistance of the normal airway in a child when the endotracheal tube is an appropriate size. Even a small amount of continuous positive airway pressure provides ventilation support and decreases effort of breathing.

PROTECTIVE VENTILATION IN HEALTHY LUNGS

For a relatively long time, the role of lung-protective ventilation has been questioned in patients with non-injured lungs. While there are no established ventilator settings for patients without lung injury, several authors suggest that, when providing an acceptable gas exchange, protective ventilator settings should be applied also in patients without lung injury, in order to protect them from VILI. Patients with normal lungs at the time of endotracheal intubation can develop lung injury over a period of hours to days, and the mechanical ventilator settings seem to influence the progress to ARDS in these patients. Even though the ARDS Network protective ventilation protocol cannot be translated directly to patients at risk for ARDS, it may be of value to guide mechanical ventilation aimed at avoiding complications from the use of too-high Vt and inadequate PEEP levels in the general ICU population. During surgical procedures, protective ventilation strategies can be as relevant as in the ICU, given that major surgery usually triggers the inflammatory response, possibly making the lungs susceptible to mechanical injury (first and second hit, respectively). Although the heterogeneity in the data concerning lung-protective ventilation and patients without lung injury has hindered its implementation in practice, the use of lung-protective ventilation should be considered in all mechanically ventilated patients, whether or not they have ARDS.

It remains a prudent approach to prevent alveolar collapse, overdistension, and exposure to high fractional inspired oxygen during the mechanical ventilation of children with normal lungs. In pediatric patients, applying PEEP to improve end-expiratory lung volume and prevent alveolar collapse is a common practice. In this context, PEEP of 5 cm H\textsubscript{2}O appears to be an appropriate starting point to further adjust based on the clinical situation. Vt becomes a more important consideration in pediatrics because of the difficulty with accurate assessment of Vt. Due to the compressibility of the ventilator circuit and inaccuracies in compensation calculations, a proximal flow sensor is recommended at the end of the endotracheal tube to obtain an accurate Vt assessment in children. However, there is evidence that even a proximal flow sensor may be inaccurate in some children and may underestimate the Vts that are actually being delivered. Furthermore, unlike in adults, in pediatrics Vt is most commonly adjusted according to actual body weight, rather than PBW. Because total lung capacity is dependent on height rather than weight, using Vt normalized to actual weight may not be an appropriate indicator of the true risk for alveolar overdistension. It can be difficult to obtain accurate height measurements in critically ill children because of their inability to stand and the high prevalence of congenital abnormalities causing scoliosis and contractures. It has
been suggested that ulnar length may be a better measurement in critically ill children and may more accurately estimate height and therefore PBW. In general, most experts agree that the VT goal in a child with normal lungs should be approximately 8 mL/kg of ideal body weight, even if formal evidence for this claim is lacking.

**ROLES OF PEEP AND TIDAL VOLUME**

Although evidence suggests that overdistension may be more injurious to the lungs than the delivery of high airway pressures, most experts recommend limiting high P_{insp} as well. The plateau pressure (P_{plat}) is the pressure during an inspiratory hold; it reflects the pressure required to overcome the elastic properties of the respiratory system. This is in contrast to the peak pressure, which also accounts for the resistive forces that are present in the tubing and respiratory system. In children with normal lungs, the peak pressure and P_{plat} should be similar since resistive forces are relatively low. Higher peak pressures in a child with normal lungs are generally required only if high pleural pressures are present, for example, due to chest wall edema or abdominal distension. A higher pleural pressure will require a higher peak pressure to maintain the same alveolar distending pressure or transpulmonary pressure during inhalation. The measurement of transpulmonary pressure requires an esophageal pressure-monitoring catheter to estimate pleural pressure. Unfortunately, these types of catheters are rarely used in pediatrics, although they are gaining popularity in adult intensive care.

In pressure control mode, the compliance of the respiratory system will dictate the VT that is delivered. In a poorly compliant respiratory system, a lower VT is delivered with the same pressure than that in a highly compliant respiratory system. Therefore, in a pressure-limited mode, VTs will decrease with worsening compliance. This is in contrast to a mode such as volume control, which provides a constant flow to achieve a set volume goal and where worsening compliance will cause increasing peak pressures. Many pediatric intensivists prefer a pressure-limited mode because it eliminates the danger of unwittingly delivering high peak pressures.

**ROLE OF DRIVING PRESSURE AND ENERGY TRAUMA**

In mechanical ventilation, driving pressure (P_{driv}) is calculated as the difference between the inspiratory P_{plat} and PEEP. Recently, P_{driv} was shown to closely predict the mortality of ARDS patients\(^9\) and the development of postoperative pulmonary complications in patients receiving mechanical ventilation during general anesthesia for surgery.\(^10\)

P_{driv} is proportional to the energy that is continuously delivered from the ventilator to the respiratory system. This concept, which was initially proposed in ARDS,\(^3\) has an attractive pathophysiologic rationale. Accordingly, lungs should be ventilated with the lowest possible energy that is compatible with an acceptable gas exchange. Importantly, this claim potentially applies not only to patients with ARDS, but also to those admitted to the ICU without lung injury and to those undergoing mechanical ventilation during general anesthesia for surgery. However, since the amount of energy delivered during mechanical ventilation depends on several settings, eg, VT and RR, it is unclear how these settings comparatively contribute to energy delivery. Also, since the amount of energy per se is not the sole determinant of the impact of
mechanical ventilation, but also the area in which the energy is distributed, intensity might better correlate with the energy trauma.

Pdriv can be easily calculated as the difference between Pplat and PEEP (Pdriv = Pplat − PEEP). The precise measurement of Pdriv requires an inspiratory hold maneuver. In many cases, a first rough estimate of Pdriv can be provided by the Pplat measured during volume control ventilation, setting a short inspiratory pause at the end of each respiratory cycle (Pdriv ≈ Pplat − PEEP), while in pressure control modes the Pinsp is similar to the Pplat; therefore, Pdriv ≈ Pinsp − PEEP. These approximate values can be used to monitor the evolution of Pdriv across time, but a precise measurement using an inspiratory hold maneuver should be performed periodically. According to the current recommendations, the clinician should reduce Pdriv as much as possible, ideally maintaining it at equal to or lower than 13 cm H₂O (Table 1, Figure 1).

<table>
<thead>
<tr>
<th>Settings</th>
<th>Values (Adults)</th>
<th>Aim</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume size (Vt)</td>
<td>6–8 mL/kg PBW</td>
<td>Prevent volutrauma</td>
<td>Lower Vt implies adjustment of higher RR to maintain adequate minute ventilation, and may increase the need for sedation. In patients with low PEEP that present low end-inspiratory stretch, lower Vt is probably not suitable.</td>
</tr>
<tr>
<td>Respiratory rate (RR)</td>
<td>Targeted at Petco₂ 35–45 mmHg</td>
<td>Ensure adequate ventilation</td>
<td>Higher levels of RR may increase risk of air trapping and intrinsic PEEP, and is typically uncomfortable.</td>
</tr>
<tr>
<td>Plateau pressure (Pplat)</td>
<td>≤20 cm H₂O</td>
<td>Prevent barotrauma</td>
<td>Adult patients with normal lungs may have low end-inspiratory stretch (~15 cm H₂O), even when they are receiving higher Vt. Patients with a stiff chest wall (eg, obese) may tolerate higher Pplat targets (~35 cm H₂O).</td>
</tr>
<tr>
<td>PEEP level</td>
<td>≥5 cm H₂O</td>
<td>Reduce atelectasis, contribute to adequate oxygenation</td>
<td>ZEEP or low levels of PEEP may promote atelectasis and atelectrauma. Higher levels of PEEP may induce hemodynamic compromise and hyperinflation. Currently, the role of PEEP for protective ventilation in non-injured lungs is not well determined.</td>
</tr>
<tr>
<td>Driving pressure</td>
<td>≤13 cm H₂O</td>
<td>Prevent barotrauma</td>
<td>Driving pressure is determined by elastic properties of the respiratory system and tidal volume. It is unclear whether it has only a predictive value, or is valuable as a target.</td>
</tr>
<tr>
<td>Recruitment maneuver (RM)</td>
<td>30–50 cm H₂O for 15–30 sec</td>
<td>Revert or prevent low end-expiratory lung volume, improve oxygenation</td>
<td>Higher levels of PEEP and the application of RM may reduce right ventricular preload and increase right ventricular afterload, causing a lower stroke volume. RMs have not been shown to improve outcome.</td>
</tr>
<tr>
<td>FiO₂ level</td>
<td>Targeted at Spo₂ 90%–92% and/or Pao₂ &gt; 55–80 mm Hg</td>
<td>Ensure adequate oxygenation and prevent hypoxia/hyperoxia</td>
<td>Both higher levels of FiO₂ and Pao₂ were associated with higher mortality rate in ICU patients. Hyperoxia may be associated with increased in-hospital mortality and brain injury in patients after cardiac arrest.</td>
</tr>
</tbody>
</table>

aValues are intended as reference only and must be adapted on an individual basis, taking all organ systems into account.

Abbreviations: ARDS, acute respiratory distress syndrome; FiO₂, fraction of inspired oxygen; Pao₂, partial arterial oxygen pressure; PBW, predicted body weight; PEEP, positive end-expiratory pressure; Petco₂, end-tidal pressure of carbon dioxide; Pplat, inspiratory airway plateau pressure; RM, recruitment maneuver; RR, respiratory rate; Spo₂, peripheral oxygen saturation; Vt, tidal volume; ZEEP, zero end-expiratory pressure.

Figure 1. Ventilation parameters
INITIAL MECHANICAL VENTILATOR SETTINGS AND MODES

Modern ICU and operating room ventilators offer several different ventilation modes. So far, evidence is lacking concerning the superiority of specific modes in patients without lung injury. Therefore, a huge heterogeneity is observed in the choice of ventilation mode in both the ICU and operating room. The clinician should be able to support the patient’s respiratory function in part with assisted modes or completely with controlled modes. Further studies are warranted to identify the advantages of specific modes over other modes in patients with healthy lungs who require mechanical ventilation.

The most commonly used controlled ventilation modes in patients without lung injury are pressure control and volume control, whereas the most common mode of assisted ventilation is pressure support. In volume control mode, the clinician sets RR and Vt, while in pressure control mode, the clinician sets the RR and the Pinsp. In most ventilators in controlled modes an inspiratory trigger based on inspiratory flow or Pinsp can be set. When the patient triggers a spontaneous breath, the ventilator delivers a cycle, similar to the mandatory breaths. The combination of controlled ventilation allowing for extra spontaneous breaths is referred to as assist control ventilation. Pressure support ventilation is a mode in which only PEEP and pressure support (or Pinsp, depending on the ventilator) is set, and each breath is initiated by the patient; an inspiratory trigger is set, and expiration is initiated when inspiratory flow decreases below a certain value, typically set as a percentage of the peak expiratory flow.

TIDAL VOLUME SIZE AND RESPIRATORY RATE

Surgical procedures can lead to postoperative pulmonary complications (PPCs), which, importantly, increase morbidity and mortality in the surgical population. Vt is a strong predictor of PPC development; the use of lower Vts during surgery is associated with better outcomes. Several randomized controlled trials that addressed intraoperative ventilation in patients without lung injury showed an improvement in outcome when using protective ventilation strategies, whereby low Vt played a major role, overwhelming that of PEEP.11
Mammals have a physiologic Vt of approximately 6.3 mL/kg, which is fairly consistent among all species, from mice to whales. In mechanical ventilation, “low Vt” usually refers to this physiologic value, differing importantly from so-called “conventional Vt” of >10 mL/kg PBW. Recent meta-analyses have concluded that the lung-protective ventilation with Vts of 5–8 mL/kg PBW in patients undergoing surgery was related to a decreased incidence of PPCs, while resulting in higher Paco₂ levels when compared with conventional ventilation with higher Vts. However, despite an increase in blood CO₂ levels, no difference in the incidence of acidosis was found in patients undergoing protective ventilation; in fact, acidosis is usually easily corrected by increasing RR in patients with normal lungs. Unquestionably, the use of lower Vts requires adjustment toward higher RRs to maintain adequate minute ventilation.

A meta-analysis addressing surgical and ICU patients reported an increase in RR during protective lung ventilation (lower Vt) compared with traditional ventilation. Regardless of differences between groups, the RR remains around 11–18 breaths/min, which is close to physiologic patterns, ie, 12–20 breaths/min. Therefore, in the experience accumulated in the context of investigations in mechanical ventilation of surgical and ICU patients without lung injury, the risk of hypercapnia was not a limiting factor hampering the use of low Vts. However, the recent attention to ventilator energy trauma could change the assumption that RR has a minor role. In fact, as explained earlier, the energy delivered from the ventilator to the respiratory system is proportional to the RR. Therefore, a reduction in Vt may be partly counteracted by an increase in RR. Furthermore, the increase in RR should be conducted cautiously, since this carries the risk of air trapping with resulting intrinsic PEEP.

In normal children, Vts during spontaneous breathing are in the range of approximately 7–8 mL/kg. The physiologic dead space, the amount of air in the lungs that does not participate in gas exchange, normally comprises approximately 30% of Vt in children and adults. Physiologic dead space is the combination of airway dead space, which is always present, and alveolar dead space, which occurs for a variety of reasons when alveolar ventilation is present without perfusion (eg, pulmonary hypertension, low cardiac output, alveolar overdistension). In a spontaneously breathing infant, the physiologic dead space is higher than in an adult due to increased airway dead space related to the relatively large head size and nasopharyngeal volume (approximately 2 mL/kg in adults versus 3 mL/kg in infants). Since, in the mechanically ventilated infant or child, much of the nasopharyngeal dead space has been removed through an artificial airway, it is important to keep in mind that other causes of increased airway dead space can dramatically increase the minute ventilation required for CO₂ elimination. Minute ventilation is the product of RR and Vt. Alveolar minute ventilation, however, is the product of RR and Vt minus dead space volume. Therefore, higher dead space volume requires either larger Vts or a higher RR to maintain the same alveolar ventilation. In mechanically ventilated children, this becomes important because of their relatively smaller Vts. For a 4-kg mechanically ventilated infant, adding just 4 mL of volume to the ventilator circuit before the Y-piece will add 1 mL/kg of additional airway dead space. Appropriate attention to this factor is imperative when managing any spontaneously breathing child on a mechanical ventilator.

**PEEP LEVELS AND RECRUITMENT MANEUVERS**
The use of low levels of PEEP, i.e., values between 0 and 5 cm H$_2$O, may favor the formation of atelectasis, especially when low Vts are used. The cyclic collapse and reopening of alveolar units has historically been considered one of the putative mechanisms leading to VILI. However, the actual relevance of this mechanism is challenged by the findings of recent studies. Apparently, atelectatic lung zones that do not undergo cyclic recruitment are even protected from the effects of mechanical ventilation on the proinflammatory response of the lung parenchyma. Unfortunately, most of the data on the use of PEEP in non-injured lungs is derived from studies on intraoperative ventilation that used bundled interventions, i.e., addressed low levels of PEEP, in combination with high Vt versus moderate to high levels of PEEP with low Vt. Thus, these studies preclude discrimination of the effect of PEEP on lung protection.

Severgnini and colleagues showed that, in abdominal non-laparoscopic surgery, a protective ventilation strategy with low Vt, 10 cm H$_2$O PEEP, and recruitment maneuvers improved the respiratory function tests and arterial oxygenation in the postoperative period. In addition, the clinical signs of pulmonary infection decreased during the first five days after surgery. In a larger trial in France, low Vt and PEEP decreased the incidence of PPCs. In this context, some authors suggest that the application of higher PEEP and recruitment maneuvers could stabilize collapsed lung regions during the respiratory cycle and counteract the effects of low Vt alone.

However, a single, large multicenter trial investigating the role of PEEP alone in moderate- to high-risk non-obese patients undergoing open abdominal surgery (Protective Ventilation using High versus Low Positive End-Expiratory Pressure [PROVHILO]) yielded surprising results. In this trial, patients were ventilated with a low Vt of 8 mL/kg PBW and were randomized to receive either low PEEP (≤2 cm H$_2$O) or high PEEP (12 cm H$_2$O) plus recruitment maneuvers following intubation and disconnection from the ventilator, and before extubation. The incidence of postoperative pulmonary complications was not different in the two arms of the trial, whereas the high-PEEP group experienced more episodes of intraoperative hypotension and needed more intravascular fluids and vasoactive drugs to stabilize the mean arterial pressure. This might be explained by the fact that PEEP reduces right ventricular preload and increases right ventricular afterload. These results suggest that PEEP alone is not able to protect the lungs during surgery. Therefore, the impact of PEEP levels and the need for recruitment maneuvers in normal lungs during surgery remains controversial. Similarly, even in ICU patients receiving mechanical ventilation for longer duration compared to surgical patients, the use of higher PEEP levels with or without recruitment maneuvers should be carefully evaluated. Compared with patients with more severely impaired respiratory function (e.g., ARDS in adults with non-injured lungs), higher levels of PEEP may show less benefit, while inducing hemodynamic impairment and static lung hyperinflation, possibly resulting in VILI.

The role of recruitment maneuvers alone for lung protection is unclear. However, when a recruitment maneuver is indicated during general anesthesia for surgery, bag squeezing should be avoided in favor of maneuvers that can be performed with the anesthesia ventilator, since it is barely controllable and may result in derecruitment when switching from bag to mechanical ventilation. More standardized and controllable recruitment maneuvers are based on stepwise increase of Vt and/or PEEP during both volume control and pressure control ventilation until the desired
opening pressure is achieved.11 Given that opening pressures may be as high as 50 cm H₂O in certain patients, stepwise increase of PEEP at a fixed Pdriv is more attractive if the anesthesia device allows pressure control ventilation. Alternatively, in some devices, a sustained lung inflation can be achieved by stepwise changes in Vt or Pinsp, or even the use of the continuous positive airway pressure mode, which can potentially avoid abrupt pressure changes often occurring with bag squeezing maneuvers.

However, patients in the ICU usually require mechanical ventilation for longer periods of time than surgical patients in the operating room. In these patients, a moderate PEEP level, of approximately 5–8 cm H₂O, can be considered to minimize atelectasis and maintain oxygenation, balancing between lung patency and static strain. Nevertheless, it is unknown whether such an approach results in improved outcome compared to lower PEEP levels.

PLATEAU PRESSURE
The Pplat at inspiration is the result of the complex interaction between PEEP, Vt, and the respiratory system compliance. Initial recommendations of the ARDS Network suggested that a Pplat below 30 cm H₂O was associated with a lower mortality when compared to values as high as 50 cm H₂O.7 In adult patients with non-injured lungs, end-inspiratory pressures are usually relatively low (eg, <15 cm H₂O), even when Vts as high as 10 mL/kg PBW are used. In patients with increased Pplats (eg, >15–20 cm H₂O), a reduction of the Vt to 6 mL/kg PBW should always be considered. This is particularly important in older patients, who usually present with a deterioration of the elastic properties of the lungs, as well as age-related impairment of the immune system, which can increase the risk of lung injury. Since the Pplat is determined also by the elastic properties of the chest wall, absolute values may differ in patients with increased intra-abdominal pressure and stiff chest.

However, studies are still necessary to identify whether targeting lower Pplats can improve outcome in patients with non-injured lungs.

FRACTION OF INSPIRED OXYGEN
An FIO₂ higher than that of room air (0.21) is usually required to maintain adequate oxygenation during mechanical ventilation in most patients, despite the use of PEEP.

The use of FIO₂ differs between patients without lung injury in the operating room and those in the ICU. During surgery, it has been claimed that higher levels of FIO₂ have decreased the incidence of wound infection and postoperative nausea and vomiting. In several studies in the operating room, after pre-oxygenation in the induction phase, the FIO₂ has been set between 0.4 and 0.5 and maintained during the entire anesthesia procedure, and higher levels have been used only as rescue, when the peripheral oxygen saturation decreased below 90%.14 In contrast, it has been claimed that the use of higher FIO₂ in the operating room has promoted reabsorption atelectasis. However, recent studies using lung imaging techniques could not show a reduction of atelectasis with lower FIO₂ in the operating room; anesthesiologists may
consider the possibility of increasing the level of \( F_{\text{IO}_2} \) rather than setting higher PEEP levels in selected patient populations.\(^ {10,11} \)

In ICU patients requiring prolonged mechanical ventilation, hypoxemia may impair outcome, while the use of excessively high \( F_{\text{IO}_2} \) may be injurious. Hyperoxia is potentially toxic, and may cause lung injury and increase oxidative stress, as well as contribute to the formation of reabsorption atelectasis with increased shunt. In spite of the deleterious effects of long-standing hyperoxia, an excessive oxygen delivery is still common in ICU patients. Both higher levels of \( F_{\text{IO}_2} \) and \( P_{\text{A}_2} \) were associated with an increase in mortality rate in these patients. Arterial hyperoxia is a common finding in ICU patients following resuscitation from cardiac arrest. In addition to the likelihood of aggravating brain injury in these patients, one multicenter cohort study showed that hyperoxia was independently associated with increased in-hospital mortality, compared with normoxia or even hypoxia. However, in a recent retrospective study of patients after cardiac arrest, the \( P_{\text{A}_2} \) obtained during the first 24 hours was not associated with in-hospital mortality. In fact, in that study, the mean \( P_{\text{A}_2} \) had a U-shaped relationship with the risk of poor neurologic outcome, suggesting the presence of a threshold \( P_{\text{A}_2} \) above or below which a detrimental effect on the neurologic function could occur. These data suggest that hypoxia and hyperoxia should both be avoided.

It has been claimed that, in ICU patients, the peripheral oxygen saturation should be kept at approximately 94%–96%, and values of 100% preferentially avoided. Currently, a strategy aiming at \( F_{\text{IO}_2} \) and \( F_{\text{IO}_2} \)-PEEP combinations to achieve \( P_{\text{A}_2} > 55–80 \) mm Hg and maintaining the peripheral oxygen saturation between 90% to 92% is under investigation. Clearly, the optimal \( F_{\text{IO}_2} \) in patients receiving mechanical ventilation in the ICU is still controversial, and clinical evidence for a formal recommendation is lacking.

**TITRATION OF MECHANICAL VENTILATION**

Patients in both the ICU and the operating room often require further adjustments during the course of mechanical ventilation. A need for an increase in \( V_t \), \( F_{\text{IO}_2} \), or PEEP usually reflects changes in the respiratory system and its ability to perform efficient gas exchanges. Several factors can lead to an impairment of the respiratory function, requiring adjustments of the ventilators, including the formation of atelectasis, fluid overload, and VILI. The latter is of particular relevance, and its occurrence should be closely monitored.

The clinical management of mechanical ventilation relies on the choice of an appropriate gas exchange target, and careful respiratory monitoring. Reasonable clinical targets for the adjustment of \( V_t \) and RR can be arterial blood pH, \( P_{\text{A}_2} \), or its surrogate, end-tidal CO\(_2\). In several trials in which \( V_t \) was fixed by the experimental setting, RR was adjusted to keep \( P_{\text{A}_2} \) between 35 and 45 mm Hg, or arterial blood pH between 7.25 and 7.45. Both in surgical and ICU patients, the main approach is to maintain normocapnia. Concerning oxygenation, \( S_{\text{PO}_2} \) can be easily monitored and can be used to tailor mechanical ventilation. Target \( S_{\text{PO}_2} \) should not exceed 96%, and possibly lower values of approximately 92% could be acceptable and more protective.\(^ {11} \)
Adjustments of PEEP levels might be necessary, and lung imaging techniques such as lung ultrasound and electrical impedance tomography can have a role in the titration of mechanical ventilation. While the effectiveness of lung recruitment maneuvers can be observed with lung ultrasound in ICU patients with damaged lungs, the role of these techniques in patients with healthy lungs needs to be further investigated.

HEMODYNAMIC EFFECTS OF POSITIVE PRESSURE VENTILATION

Mechanical ventilation can have significant consequences on the hemodynamic performance. Positive pressure decreases the preload to the right ventricle and decreases afterload to the left ventricle. Right ventricle afterload can either increase or decrease depending on the end-expiratory lung volume and Vt achieved with positive pressure ventilation. If PEEP recruits collapsed alveoli, pulmonary vascular resistance will fall. On the other hand, if positive pressure ventilation leads to alveolar overdistension, pulmonary vascular resistance will increase. These differences are caused by the effect of positive pressure on alveolar vessels adjacent to the alveolar wall, and extra-alveolar vessels, which are large vessels in the interstitium. Total pulmonary vascular resistance is affected by both type of vessels. With an atelectatic lung, extra-alveolar vessels have a tendency to collapse, whereas with an overdistended lung, alveolar vessels collapse. Therefore, the nadir of pulmonary vascular resistance is around the functional residual capacity or the end-expiratory lung volume for normal tidal breathing.

In hemodynamically stable mechanically ventilated children, it has been demonstrated that cardiac output does fall with increasing PEEP from 0 to 12 cm H$_2$O regardless of the optimal dynamic compliance, but the decrease in cardiac output was not clinically relevant (10%). In the child with hemodynamic compromise, however, ventilator settings and changes should be carefully considered for their impact on cardiac output. Often, in children with hemodynamic compromise and relatively normal lungs, simply placing a child on mechanical ventilation and eliminating the work performed by the child’s respiratory muscles is enough to significantly decrease oxygen consumption.

Children with congenital heart disease are often ventilated during the perioperative period. This patient population has unique considerations, particularly for those with a single functional ventricle undergoing three-stage palliation surgeries. In the first stage, blood flow to the lungs and the body are both dependent on the same ventricle and ideally balanced. When pulmonary vascular resistance or systemic vascular resistance changes, this balance can disintegrate and cause increased cardiac output requirements to meet oxygen delivery demands. Ventilator strategies to minimize high pressures and inspiratory time while promoting mild hyperventilation can decrease pulmonary vascular resistance. This is often accomplished using higher Vts (10 mL/kg) and a lower set ventilator rate. On the other hand, when pulmonary blood flow is excessive, strategies to cause mild hypoventilation can increase pulmonary vascular resistance and promote systemic blood flow. This often requires neuromuscular blockade. In the final stage of palliation (Fontan surgery), blood flow to the lungs is completely passive, making strategies to optimize pulmonary blood flow during mechanical ventilation, such as low airway pressures, spontaneous breathing, and mild hypoventilation, even more important.
CONSIDERATIONS FOR THE MANAGEMENT OF PEDIATRIC PATIENTS

In addition to the specific aspects already mentioned, there are several generic anatomic and physiologic differences between infants, children, and adults that must be taken into account in order to optimize the ventilatory management of these patients.

AIRWAY DIFFERENCES RELEVANT TO ENDOTRACHEAL TUBE MANAGEMENT

Infants and children have a funnel-shaped larynx with a trachea that is much shorter and smaller in diameter than adults. Until age 8–10 years, a child’s airway is narrowest at the level of the cricoid cartilage. Because of this, endotracheal tube size in children should be carefully considered. The most commonly used formula to estimate endotracheal tube size is the modified Cole formula: age/4 + 4 mm inner diameter. Previously, it was thought that children younger than eight years should not be managed with cuffed endotracheal tubes because the cuff resides in the narrowest region of the airway. Evidence supports that, with proper management, a cuffed endotracheal tube can be used safely in infants and children and does not increase the risk of post-extubation stridor or subglottic stenosis. The size chosen when a cuffed endotracheal tube is used should be 0.5 mm less than the modified Cole formula suggests for age. If subglottic narrowing is suspected, a smaller uncuffed endotracheal tube of the size predicted for age may also be necessary. Extra-long endotracheal tubes are sometimes needed in this situation. More important than the size chosen is an assessment for the presence of a low leak pressure upon endotracheal tube insertion, characterizing appropriate room around the endotracheal tube in the subglottic area. A recent study examining risk factors for upper airway obstruction in children found that low cuff leak volume and high pre-extubation leak pressure were independently associated with post-extubation upper airway obstruction in children managed with cuffed endotracheal tubes.

In addition to the risk of subglottic stenosis, infants and children are also at higher risk of endotracheal tube dislodgement. The average distance from vocal cords to carina in an infant younger than three months is 5 cm. Therefore, there is less flexibility in placement of an endotracheal tube in a child, and relatively small movements of the endotracheal tube by neck extension or flexion may cause either bronchial intubation or an unplanned extubation. In a study examining with fiberoptic bronchoscopy the endotracheal tube movement in children between the ages of 16 and 19 months, head extension caused the endotracheal tube to move a mean of 1.7 cm toward the vocal cords, and head flexion caused the endotracheal tube to move a mean of 0.9 cm toward the carina. The correct insertion depth of an endotracheal tube can be somewhat difficult to determine in children. Practitioners commonly use a general rule of insertion of 3 cm x the size of the endotracheal tube or insertion until the black glottic marker on the endotracheal tube is reached. This generally allows for reasonable tracheal placement below the thoracic inlet and above the carina. However, it is important to note that, in children mechanically ventilated with a smaller endotracheal tube for subglottic narrowing, the insertion depth should be based on the recommended tube size for a child with a normal airway.

PHYSIOLOGY DIFFERENCES RELEVANT TO MECHANICAL VENTILATION

Respiratory anatomy and physiology change remarkably over the first several years.
of life. Any infant or young child is at high risk for atelectasis during mechanical ventilation. Newborns have a highly compliant chest wall. From birth until approximately age two years, as bone ossification and calcification of cartilage progress, chest wall compliance gradually decreases to levels similar to that of an adult. A more compliant chest wall increases the work of breathing an infant must perform compared to an adult because there is less mechanical efficiency due to decreased chest wall recoil. Infants have a lower functional residual capacity (FRC) relative to total lung capacity due to this lack of chest wall recoil. FRC during normal breathing in an infant is often similar to the closing capacity, or the volume at which the small airways start to collapse on exhalation.

Infants have normal compensatory mechanisms to limit atelectasis and increase their end-expiratory lung volumes. They have a shorter expiratory time with expiratory braking due to contraction of the glottis muscles, and they maintain tonic activity of the diaphragm to slow exhalation. Closing capacity can be higher than FRC until around age six years. Anesthetized infants and children have decreased muscle tone and inability to perform compensatory mechanisms to increase end-expiratory lung volume, placing them at even higher risk of atelectasis, with end-expiratory lung volume often considerably lower than baseline FRC. Furthermore, interalveolar connections (pores of Kohn) develop at age one to two years, and alveolar bronchiole connections (canals of Lambert) develop at around age three years; these mechanisms help prevent collapse of alveoli through alternative pathways of ventilation that are not present at birth.

Most alveolarization is thought to occur during the first eight years of life; however, there is evidence suggesting that this process might continue through adolescence. Newborns have approximately 10% the number of alveoli that an adult has. Much of the increase in total lung capacity following birth is due to an increase in the number of primary alveoli. This rapid growth of the distal lung with increasing age is in contrast to relatively steady changes in central airway dimensions. The conducting capacity of the peripheral airways is five times higher than the central airways of adults; however, in children it is approximately the same. For these reasons, in addition to an overall smaller airway diameter, infants and children have a higher airway resistance than adults. A similar amount of edema will increase the resistance of a child’s airway exponentially compared with that of an adult. A small airway diameter also makes a child’s airways more prone to partial or complete obstruction with resultant air trapping or collapse. Higher airway resistance further increases the work of breathing for infants.

Children and infants are also more subject to respiratory muscle fatigue, which is important to consider when weaning from mechanical ventilation. Infants exert more work of breathing for a comparable Vt than adults because of their inefficient respiratory mechanics. In addition to the high chest wall compliance, the anatomy of the rib cage and diaphragm limit their ability to function efficiently. The ribs are positioned more horizontally than they are in adults, limiting thoracic expansion and the “bucket handle effect.” The diaphragm, which is the major muscle of ventilation in children, is relatively flat, rather than domed, causing its function to be more of a bellows than a piston fashion. Infants are prone to muscle fatigue since they have a lower percentage of type 1, slow-twitch, fatigue-resistant muscle fibers in their diaphragm. Abdominal distension will affect the function of an infant’s diaphragm to a larger degree than an adult’s. Furthermore, infants are at an additional disadvantage
because they have a higher metabolic rate per kilogram than adults, which therefore requires a higher oxygen demand and higher minute ventilation per kilogram. A normal infant or child has a higher RR than an adult for this reason.

KEY POINTS

- Mechanical ventilation is a life-saving intervention that can also cause injury to the lungs.
- In children and adults with normal lungs, it is imperative to understand the physiology of lungs and the mechanisms of VILI in order to titrate mechanical ventilation.
- Current recommended approaches include the use of low tidal volume, moderate levels of positive end-expiratory pressure and $F_{IO_2}$, and low driving pressure, but further studies are still required to determine the best combination of these protective measures in patients without lung injury.

References

Chapter 9

STRATEGIES FOR VENTILATOR DISCONTINUANCE

Dean Hess RRT, PhD, FCCM, and Adrienne Randolph, MD, MS

Objectives

- Assess potential readiness for ventilator discontinuation
- Discuss the role of, and indications for, weaning parameters
- Discuss methods and evidence for implementing spontaneous awakening and spontaneous breathing trials
- Describe ventilator modes used in the ventilator discontinuation process
- Distinguish between ventilator liberation and extubation
- Discuss the use of ventilator discontinuation protocol
- Discuss criteria used to assess readiness for extubation
- Explain the role of noninvasive ventilation, high-flow nasal cannula, and cough assist to reduce the risk of extubation failure

INTRODUCTION

Many strategies have been used in the process of ventilator discontinuance with the goal of ultimately liberating the patient from mechanical ventilator support. One strategy is weaning, in which the amount of ventilator support is gradually withdrawn while assessing patient tolerance. Many years ago, much effort was put into developing weaning strategies for patients with acute respiratory failure, based on the assumption that patients needed a period of time to recover their strength and rebuild respiratory muscles. In the past two decades, rigorous studies have revealed that most patients with acute respiratory failure do not require weaning per se, but rather treatment of the underlying disease process and recognition of the time when mechanical ventilation is no longer necessary. Most important to the process of identifying when a patient can be liberated from the ventilator is a spontaneous breathing trial (SBT). For patients who fail an SBT, it is important to identify and address possible causes underlying the failure. Assessment for ventilator liberation is not always the same as assessment for extubation; indeed, some patients with airway or secretion management issues can be liberated from mechanical ventilation but may still need an artificial airway. In recent years, newer respiratory modalities have become available to reduce the risk of reintubation, including noninvasive ventilation (NIV), high-flow nasal cannula (HFNC), and cough assist devices.

In 2001, a collective task force of three professional societies published Evidence-Based Guidelines for Weaning and Discontinuing Ventilatory Support. From this group’s work came the 12 recommendations in Table 1. In 2007, the recommendation of an international consensus conference provided additional recommendations regarding management of the ventilator discontinuation process (Table 2). This group suggested that ventilator discontinuation could be categorized as simple, difficult, or prolonged (Table 3). In one study, a prolonged ventilator...
discontinuation process was reported as an independent risk factor in adults for longer intensive care unit (ICU) stay and hospital mortality, but not one-year mortality. In this study of adult patients, 30% were in the simple group, 40% were in the difficult group, and 30% were in the prolonged group.

**TABLE 1. Evidence-Based Guidelines for Discontinuing Ventilatory Support**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation 1:</strong></td>
<td>In patients requiring mechanical ventilation for more than 24 hours, a search should be undertaken for all causes that may be contributing to ventilator dependence. This is particularly true for patients who have failed attempts at withdrawing mechanical ventilation. Reversing all possible ventilatory and nonventilatory issues should be an integral part of the ventilator discontinuation process.</td>
</tr>
<tr>
<td><strong>Recommendation 2:</strong></td>
<td>Patients receiving mechanical ventilation for respiratory failure should undergo a formal assessment of discontinuation potential if the following criteria are satisfied: 1) evidence for some reversal of the underlying cause for respiratory failure, 2) adequate oxygenation and pH, 3) hemodynamic stability, and 4) the capability to initiate an inspiratory effort.</td>
</tr>
<tr>
<td><strong>Recommendation 3:</strong></td>
<td>Formal discontinuation assessments for patients receiving mechanical ventilation for respiratory failure should be performed during spontaneous breathing rather than while the patient is still receiving substantial ventilatory support. An initial brief period of spontaneous breathing can be used to assess the capability of continuing on to a formal spontaneous breathing trial (SBT). The criteria with which to assess patient tolerance during SBTs are respiratory pattern, adequacy of gas exchange, hemodynamic stability, and subjective comfort. The tolerance of SBTs lasting 30 to 120 minutes should prompt consideration for permanent ventilator discontinuation.</td>
</tr>
<tr>
<td><strong>Recommendation 4:</strong></td>
<td>The removal of the artificial airway from a patient who has successfully been discontinued from ventilatory support should be based on assessments of airway patency and the patient’s ability to protect the airway.</td>
</tr>
<tr>
<td><strong>Recommendation 5:</strong></td>
<td>For patients who are receiving mechanical ventilation for respiratory failure and who fail an SBT, the cause for the SBT failure should be determined. Once reversible causes for failure are corrected, subsequent SBTs should be performed every 24 hours.</td>
</tr>
<tr>
<td><strong>Recommendation 6:</strong></td>
<td>Patients receiving mechanical ventilation for respiratory failure who fail an SBT should receive a stable, nonfatiguing, and comfortable form of ventilatory support.</td>
</tr>
<tr>
<td><strong>Recommendation 7:</strong></td>
<td>Anesthesia/sedation strategies and ventilator management aimed at early extubation should be used in postsurgical patients.</td>
</tr>
<tr>
<td><strong>Recommendation 8:</strong></td>
<td>Weaning/discontinuation protocols that are designed for nonphysician healthcare professionals should be developed and implemented by intensive care unit staff. Protocols aimed at optimizing sedation also should be developed and implemented.</td>
</tr>
<tr>
<td><strong>Recommendation 9:</strong></td>
<td>Tracheostomy should be considered after an initial period of stabilization on the ventilator when it becomes apparent that the patient will require prolonged ventilator assistance. Tracheostomy then should be performed when the patient appears likely to gain one or more of the benefits ascribed to the procedure. Patients who may derive particular benefit from early tracheostomy are those who require high levels of sedation to tolerate an endotracheal tube; those with marginal respiratory mechanics (often manifested as tachypnea) in whom a tracheostomy tube having lower resistance might reduce the risk of muscle overload; those who might derive psychological benefit from the ability to eat orally, communicate by articulated speech, and experience enhanced mobility; and those in whom enhanced mobility may assist physical therapy efforts.</td>
</tr>
<tr>
<td><strong>Recommendation 10:</strong></td>
<td>Unless there is evidence for clearly irreversible disease (eg, high spinal cord injury or advanced amyotrophic lateral sclerosis), a patient requiring prolonged mechanical ventilatory support for respiratory failure should not be considered permanently ventilator dependent until three months of ventilator liberation attempts have failed.</td>
</tr>
<tr>
<td><strong>Recommendation 11:</strong></td>
<td>Critical care practitioners should familiarize themselves with facilities in their communities, or units in their hospitals, that specialize in managing patients who require prolonged dependence on mechanical ventilation. Such familiarization should include reviewing published peer-reviewed data from those units, if available. When medically stable for transfer, patients who have failed ventilator discontinuation attempts in the intensive care unit should be transferred to those facilities that have demonstrated success and safety in accomplishing ventilator discontinuation.</td>
</tr>
<tr>
<td><strong>Recommendation 12:</strong></td>
<td>Ventilator liberation strategies in the prolonged mechanical ventilation patient should be slow paced and should include gradually lengthening self-breathing trials.</td>
</tr>
</tbody>
</table>
TABLE 2. Recommendations of an International Consensus Conference Regarding Management of the Ventilator Discontinuation Process in Adults

**Recommendation 1:** Patients should be categorized into three groups based on the difficulty and duration of the weaning process.

**Recommendation 2:** The ventilator discontinuation process should be considered as early as possible.

**Recommendation 3:** A spontaneous breathing trial (SBT) is the major diagnostic test to determine when a patient can be successfully extubated.

**Recommendation 4:** The initial SBT should last 30 minutes and should consist of either T-tube breathing or low levels of pressure support.

**Recommendation 5:** Pressure support or continuous mandatory ventilation (assist/control) is favored in patients failing an SBT.

**Recommendation 6:** Noninvasive ventilation should be considered in selected patients to shorten the duration of intubation, but should not be routinely used as a tool for extubation failure.


TABLE 3. Classification of Patients According to the Ventilator Discontinuation Process

<table>
<thead>
<tr>
<th>Simple</th>
<th>Patients who successfully extubate after the first spontaneous breathing trial (SBT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult</td>
<td>Patients who fail the initial SBT and require up to three SBTs or as long as seven days from the first SBT to achieve successful ventilator liberation</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Patients who fail at least three SBTs or require more than seven days from the first SBT to achieve successful ventilator discontinuation</td>
</tr>
</tbody>
</table>

BRIEF CASE STUDIES

**Adult**

A 68-year-old man with a chronic obstructive pulmonary disease (COPD) exacerbation is intubated following NIV failure. He is treated with short-acting bronchodilators, steroids, and antibiotics. On the second day following intubation, oxygen saturation ($SpO_2$) is 92% on fraction of inspired oxygen ($FiO_2$) 0.3 with positive end-expiratory pressure (PEEP) 5 cm H$_2$O. No auto-PEEP is measured. He tolerates a spontaneous awakening trial (SAT) and an SBT, and is extubated to nasal cannula oxygen at 2 L/min. About four hours after extubation, respiratory failure ensues and he is reintubated. What can be done to maximize the likelihood of successful extubation in the future?

**Pediatric**

A three-month-old, previously healthy, 5-kg infant was intubated with a 3.5-mm cuffed endotracheal tube for acute respiratory failure after developing pneumonia.
and acute lung injury from an influenza B virus infection. The infant was initially profoundly hypoxemic and paralyzed, and was managed using lung-protective ventilation with pressure-regulated volume control. On days five to seven, the infant's oxygenation slowly improved. The infant tolerated a reduction of PEEP from 12 to 6 cm H$_2$O and F$_{IO_2}$ from 0.6 to 0.4, with Spo$_2$ remaining 92% to 96%. Paralysis was discontinued six hours ago, sedation was weaned this morning, and the infant is starting to take spontaneous breaths. How should the clinician assess when the infant is ready for extubation?

**ASSESSING READINESS FOR VENTILATOR DISCONTINUATION**

*Improvement in Underlying Disease Process*

An appropriate (lung-protective) level of respiratory support should be provided while aggressively treating the underlying disease process that resulted in the need for ventilatory support (eg, diuresis, antimicrobials). Once adequate recovery from acute respiratory failure occurs, the process of discontinuing mechanical ventilatory support should begin. Both subjective and objective criteria are used to assess recovery; these include improvements in gas exchange, mental status, neuromuscular function, and radiographic findings. It should also be appreciated that improvement in the underlying disease process might not occur in some patients, such as those with progressive neuromuscular disease. In this case, options for prolonged mechanical ventilation should be considered.

*Gas Exchange*

Adequate gas exchange is a consideration when assessing readiness for ventilator discontinuation. Generally, in adults, Spo$_2$ should be >92%, with F$_{IO_2}$ ≤0.5 and PEEP ≤8 cm H$_2$O. In infants and young children, Spo$_2$ should optimally be ≥95% on F$_{IO_2}$ ≤0.6 with PEEP ≤7 cm H$_2$O. In adults, ventilation should be such that pH is >7.25 with an acceptable minute ventilation (<10 L/min). If high minute ventilation is required (high dead space, high CO$_2$ production), it is less likely that patients will be able to sustain this with spontaneous breathing.

*Sedation*

The ability to initiate an inspiratory effort is necessary before ventilator discontinuation can proceed. The level of sedation often determines this. Thus, tolerance of an SAT often precedes the formal assessment of ventilator discontinuation by an SBT. Patients should be assessed daily with an SAT (Table 4). Patients are considered to have passed the SAT if they open their eyes to verbal stimuli. If the patient fails the SAT, sedation is restarted at half the previous dose and titrated to effect using an objective sedation score such as the Sedation-Agitation Scale or Richmond Agitation-Sedation Scale. The State Behavioral Scale is a customized sedation scale for children. Another strategy uses targeted sedation rather than an SAT. In one study in adults, the addition of a daily SAT did not reduce the duration of mechanical ventilation or ICU stay when compared to sedation targeted at a Sedation-Agitation Scale score of 3 or 4 or a Richmond Agitation-Sedation Scale score of −3 to 0. In adults, sedation strategies using non-benzodiazepine sedatives (propofol or dexmedetomidine) are preferred over
sedation with benzodiazepines. In a large real-world cohort, propofol and dexmedetomidine were associated with less time to extubation compared to benzodiazepines, but dexmedetomidine was associated with less time to extubation compared to propofol. Use of propofol as a sedative must be restricted in children because of the risk of propofol infusion syndrome.

### TABLE 4. Spontaneous Awakening Trial for Adult Patients

<table>
<thead>
<tr>
<th>Safety Screen</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No active seizures</td>
</tr>
<tr>
<td>• No alcohol or drug withdrawal</td>
</tr>
<tr>
<td>• No agitation</td>
</tr>
<tr>
<td>• No paralytics</td>
</tr>
<tr>
<td>• No myocardial ischemia</td>
</tr>
<tr>
<td>• Normal intracranial pressure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anxiety, agitation, pain</td>
</tr>
<tr>
<td>• Respiratory rate &gt;35 breaths/min</td>
</tr>
<tr>
<td>• Oxygen saturation by pulse oximetry &lt;88%</td>
</tr>
<tr>
<td>• Respiratory distress</td>
</tr>
<tr>
<td>• Acute arrhythmia</td>
</tr>
</tbody>
</table>

### Hemodynamic Stability

Adult and pediatric patients should be hemodynamically stable before attempting to discontinue mechanical ventilation. Hemodynamic stability is defined as absence of active myocardial ischemia and absence of clinically significant hypotension (ie, requiring no vasopressor therapy or only low-dose). In adults, serum B-type natriuretic peptide (BNP) is a marker of fluid overload; it can be elevated due to fluid overload and it can rise during an SBT due to left ventricular failure. In one study, the use of BNP level to guide fluid/diuretic therapy resulted in a more negative fluid balance compared to usual care and was associated with more rapid ventilator discontinuation and a greater number of ventilator-free days. A serum BNP >200 pg/mL triggered fluid restriction and diuresis in the intervention group.

### WEANING PARAMETERS

Many weaning parameters have been introduced over the years, the intent of which are to predict the potential for success of ventilator liberation (Table 5). No weaning parameter is 100% accurate in identifying adult patients who can be successfully liberated from the ventilator. A rigorous review of evidence for pediatric patients also failed to identify reliable and accurate methods for assessing readiness for weaning or predicting extubation success. Therefore, high-level evidence supporting the use of weaning parameters is lacking. One predictor of weaning success for adult patients is the rapid shallow breathing index (RSBI). The RSBI is determined by dividing the respiratory rate by the tidal volume in liters, determined one minute after removing respiratory support. An RSBI ≤105 suggests that the likelihood of successful liberation is high; an RSBI >105 suggests that the likelihood of liberation failure is high. However, the RSBI may not be as predictive of ventilator liberation as originally reported. In one study, use of the RSBI resulted in a delay to successful...
Thus, overreliance on weaning parameters may result in prolonged time on the ventilator. The low likelihood ratios reported for weaning parameters indicate that their clinical value in individual patients is low.

**TABLE 5. Weaning Parameters That Have Been Used to Predict Ventilator Liberation in Adult Patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory drive: $P_{0.1}$</td>
<td>$&lt; 6$ cm H$_2$O</td>
</tr>
<tr>
<td>Respiratory muscle strength:</td>
<td>Vital capacity $&gt; 10$ mL/kg, maximum inspiratory pressure $&lt;-30$ cm H$_2$O</td>
</tr>
<tr>
<td>Ventilatory performance:</td>
<td>Minute ventilation $&lt; 10$ L/min, respiratory rate $&lt; 30$ breaths/min, rapid shallow breathing index $&lt; 105$.</td>
</tr>
</tbody>
</table>

**SPONTANEOUS BREATHING TRIALS**

Two prospective, randomized, controlled trials\(^{14,15}\) compared synchronized intermittent mandatory ventilation weaning (gradual reduction in mandatory breath rate), pressure support (PS) weaning (gradual reduction in the level of PS), and daily (or twice daily) SBT. In these studies, an SBT was performed after meeting screening criteria. In both studies, the majority of patients were successfully extubated after the first SBT. In the minority of patients who failed the initial SBT, no difference in duration of mechanical ventilation was seen between the SBT and PS methods. However, SBT and PS were superior to synchronized intermittent mandatory ventilation in adults. Patients who tolerate an SBT for 30 to 120 minutes should be considered liberated from ventilatory support.

**T-piece**

The conventional SBT for adults is performed with a T-piece connected to the endotracheal tube providing humidified gas. Humidification is usually provided as a heated or cool aerosol from a large-volume nebulizer. For patients with reactive airways, this might induce bronchospasm; therefore, a humidification system that does not generate an aerosol should be used (heated humidifier). Passive humidifiers (heat and moisture exchangers) should be avoided because of their dead space and resistive workload. Due to the smaller diameter and higher resistance of pediatric endotracheal tubes, T-piece trials are not often used.

**On-Ventilator Approaches**

The SBT can be conducted without disconnecting the adult patient from the ventilator. Modern ventilators are very responsive to patient effort. Thus, if the ventilator is set for a PEEP of 0 and a PS of 0, it is similar to a T-piece. This approach has the advantages of requiring no additional equipment, the ability to quickly reestablish ventilatory support if the patient fails the SBT, and the availability of monitoring functions and alarms on the ventilator.

The SBT can be performed with a low level of continuous positive airway pressure (CPAP) (5 cm H$_2$O), with a low level of PS (5 to 10 cm H$_2$O), or with the use of inspiratory pressure automatically titrated to overcome endotracheal tube resistance (ie, tube compensation). A low level of PS might overcome the resistance to breathing through the artificial airway. Tube compensation adjusts the level of PS according to the size of the endotracheal tube and inspiratory flow; it compensates
for the resistance through the endotracheal tube. The upper airway, however, is typically swollen and inflamed in an intubated patient, such that the resistance through the upper airway after extubation may be similar to that seen with the endotracheal tube in place. Similar outcomes of the SBT have been reported with a T-piece and with 7 cm H$_2$O PS, and with or without tube compensation.

CPAP of 5 cm H$_2$O is commonly used during an SBT, in order to maintain lung volume. Some argue that CPAP of 5 cm H$_2$O is physiologic, but there is no such thing as physiologic PEEP. In some ICUs, the SBT is performed using a PS of 5 cm H$_2$O and CPAP of 5 cm H$_2$O. In patients with marginal left ventricular function, a low level of positive intrathoracic pressure may support the failing heart, such that these patients might tolerate a CPAP trial but then develop congestive heart failure when extubated. A low level of CPAP might also counterbalance auto-PEEP and facilitate breath triggering in patients with COPD, resulting in a successful SBT, but respiratory failure soon after extubation. In one study, PS and PS/PEEP markedly modified breathing pattern, inspiratory muscle effort, and cardiovascular response compared to a T-piece. In another study, tube compensation with 5 cm H$_2$O PEEP, and 5 cm H$_2$O PS with 5 cm H$_2$O PEEP, reduced the predictive performance of breathing pattern variability, compared to that with a T-piece trial. This finding suggests that the SBT in adult patients should be performed without PS or PEEP. In many patients, the approach to the SBT, whether performed without support or with a low level of support, might not affect the outcome. However, there may be an important number of patients in whom the SBT is successful with a low level of support, but not if performed without support. These patients will be subjected to the potential for failed extubation if the SBT is done using minimal ventilator settings. Thus, it is recommended that the SBT, again, in adults, is conducted without ventilatory support, either with the ventilator set to a PS of 0 and a PEEP of 0, or with a T-piece.

Children intubated for acute respiratory failure also should receive an SBT. In a multicenter study of 182 ventilated pediatric patients, an SBT (extubation readiness test) was performed for children meeting screening criteria. Patients were placed on PEEP ≤5 or F$_{I\text{O}_2}$ ≤0.5. If they maintained Sp$_{O_2}$ >94%, they were then converted to PS titrated to the size of the endotracheal tube (eg, 3.0–3.5 mm, then PS = 10 cm H$_2$O; ≥5.0 mm, then PS = 6 cm H$_2$O). Of patients passing the test, 88% were extubated, and the great majority (87%) required no additional ventilator support.

Recognition of SBT Failure

A failed SBT is discomforting for the patient, and it might induce significant cardiopulmonary distress. Criteria for discontinuation of an SBT in adults include:

- Tachypnea (respiratory rate >35 breaths/min for >5 minutes)
- Hypoxemia (Sp$_{O_2}$ below 90%)
- Tachycardia (heart rate >140 beats/min or a sustained increase above 20% of baseline)
- Bradycardia (sustained decrease in heart rate >20%)
- Hypertension (systolic blood pressure >180 mm Hg)
- Hypotension (systolic blood pressure <90 mm Hg)
- Agitation, diaphoresis, anxiety
Similar criteria are used for children, but the parameters for tachycardia and tachypnea vary by age given that young children have higher heart rates and respiratory rates.\textsuperscript{22}

In some patients, these factors are not caused by SBT failure and can be treated with verbal reassurance or pharmacologic support. When SBT failure is recognized, ventilatory support should be reestablished. The goal is to provide sufficient support for patient comfort. The mode and specific settings are less important than patient comfort, providing that the settings are safe.

**APPROACHES TO FAILED SBT**

After the failed SBT, and after the patient has been returned to comfortable ventilator settings, the cause of the failed SBT should be identified and corrected. With correction of the cause of the failure, another SBT is done 24 hours after the failed one. There are a number of physiologic and technical reasons that patients fail an SBT; these should be systematically explored and treated as appropriate. A failed SBT in adults is often caused by an imbalance between the load on respiratory muscles and the capability of the muscles to meet that load, as follows:

- Excessive respiratory muscle load: High airway resistance and low compliance.
- Auto-PEEP: Increases the pleural pressure needed to initiate inhalation.
- Cardiac dysfunction: Left heart failure when intrathoracic pressure decreases with the transition for positive pressure ventilation to spontaneous breathing.
- Respiratory drive: Increase (acidosis, pain) or decrease (narcotics) in respiratory drive. In children, over-sedation is the most common cause of a failed SBT.\textsuperscript{22}
- Respiratory muscle weakness: Preexisting (myasthenia gravis, muscular dystrophy, amyotrophic lateral sclerosis) or acquired (critical care myopathy, diaphragm paralysis).
- Electrolyte imbalance: Low levels of potassium, magnesium, phosphate, and calcium can impair ventilatory muscle function.
- Nutritional support: Care should be taken to avoid overfeeding, which elevates carbon dioxide production.
- Fever and infection: Increases oxygen consumption and carbon dioxide production, resulting in an increased ventilatory requirement.
- Major organ system failure: Renal failure, neurologic impairment.
- Technical issues: Endotracheal tube obstruction, malposition of endotracheal tube or tracheostomy tube.

**VENTILATOR DISCONTINUATION PROTOCOLS**

Protocols include the important instructions to ensure that a consistent approach is used to evaluate patients implementing best evidence and advice from clinical experts. Protocols are tools that complement and enhance, but do not replace, clinical decision-making.\textsuperscript{23} Successful protocols are developed by multidisciplinary teams based on the specific patient population, fit the culture of the ICU, and are implemented by respiratory therapists and nurses empowered to make bedside clinical decisions while communicating with the physician team. Ventilator discontinuation protocols are common in adult ICUs in the United States,\textsuperscript{24} and are increasingly used in pediatric ICUs. Elements of a ventilator discontinuation protocol are shown in Figure 1.\textsuperscript{25}
**Figure 1.** An approach to discontinuation of mechanical ventilation that stresses treatment of the underlying disease process, stopping sedation, and performing spontaneous breathing trials.

The details of this approach can be used to develop specific instructions for a ventilator discontinuation protocol to fit the culture of an individual ICU.


Blackwood et al.26 conducted a Cochrane systematic review and meta-analysis on the use of ventilator discontinuation protocols. The review comprised 11 trials that included 1,971 patients. Compared with usual care, the mean duration of mechanical ventilation in the protocol group was reduced by 25% (95% CI, 9%–39%), the duration of weaning was reduced by 78% (31%–93%), and ICU stay by 10% (2%–19%). The results of this systematic review support the use of ventilator discontinuation protocols.

**AUTOMATED SYSTEMS**

Automated systems have been developed for closed-loop control to enable ventilators to perform basic and advanced functions while providing life support. Staffing shortages, increased demand for care, and failure of clinicians to use evidence-based practices have established the rationale for automated weaning using software within the ventilator.27 The most common of these modes are adaptive pressure control (APC), Automode, adaptive support ventilation (ASV), and SmartCare/PS.

APC adjusts the inspiratory pressure to deliver a minimum target tidal volume. Common names for this mode include pressure-regulated volume control, adaptive...
pressure ventilation, volume control+, volume-targeted pressure control, pressure-controlled volume-guaranteed, and volume support. Volume support is a spontaneous mode, whereas the others are mandatory modes. If tidal volume decreases below the target, the ventilator increases the inspiratory pressure. If tidal volume is greater than the target, the ventilator decreases inspiratory pressure. One could imagine that this could result in the ventilator weaning the amount of support as respiratory failure improves.

Automode is available on the Maquet ventilator. It uses an algorithm to switch from a mandatory mode (eg, pressure control) to a spontaneous mode such as PS, based on the detection of patient triggering. The mode switches from spontaneous to mandatory with prolonged apnea (>12 seconds). Other possible mode switches are from volume control to volume support ventilation or from pressure-regulated volume control to volume support.

ASV is available on the Hamilton ventilator. It is a closed-loop mode that adjusts inspiratory pressure and mandatory breath rate to maintain preset minimum minute ventilation with an optimal respiratory pattern. The clinician selects ideal body weight, percentage of minute ventilation desired (25% to 350% of 0.1 L/min/kg), and maximal inspiratory pressure. ASV is applied as pressure control (PC), with optimal tidal volume based on the selected minimum minute ventilation, dead space calculated from ideal body weight, and expiratory time constant (Figure 2). When the patient makes an inspiratory effort, ASV switches from PC to PS, with the level of PS adapted to the patient’s respiratory rate and tidal volume to achieve the desired minute ventilation.

Figure 2. Adaptive support ventilation adjusts both the inspiratory pressure of mandatory and/or spontaneous breaths and the mandatory breath rate to maintain the desired breathing pattern

Abbreviations: f, respiratory frequency; Pinsp, inspiratory pressure; VT, tidal volume.

Reproduced with permission Branson RD. Modes to facilitate ventilator weaning. Respir Care. 2012;57(10):1635-1648. Copyright © 2012 by Daedalus Enterprises Inc.

Smartcare/PS is available on the Dräger ventilator. This mode provides closed-loop control of PS in response to respiratory rate, tidal volume, and end-tidal carbon
dioxide, to maintain the patient in a respiratory zone of comfort. SmartCare/PS adjusts PS to maintain the patient in a normal range of ventilation, defined as tidal volume >300 mL, respiratory rate 15 to 30 breaths/min, and partial pressure of end-tidal CO₂ (P_{ETCO₂}) <55 mm Hg (assuming a patient weighing >55 kg without COPD or neurologic injury). The P_{ETCO₂} target is <65 mm Hg for COPD and <45 mm Hg for neurologic injury. Outside this range, SmartCare/PS defines other conditions and manipulates the PS based on the current value, the clinician-input parameters, and the patient’s breathing pattern (Table 6). The SmartCare/PS system divides weaning into three phases: 1) stabilizing the patient within the respiratory zone of comfort, 2) decreasing PS while maintaining the patient within the comfort zone, and 3) testing for extubation readiness by monitoring the patient at the lowest level of PS. Different from other closed-loop approaches that make breath-by-breath changes, Smartcare/PS changes settings after several minutes. When the patient is weaned to a low level of PS, an SBT is performed automatically, during which the patient is observed over a period of time at a low support level. If the patient fails the SBT, the ventilator adjusts support as required. If the patient passes the SBT, SmartCare/PS alerts the clinician to “Consider Separation!”

### Table 6. Defined Conditions Based on Tidal Volume, Respiratory Rate, P_{ETCO₂}, and the Ventilator Response During SmartCare/PS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Parameters</th>
<th>PS Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ventilation</td>
<td>f 15–30 breaths/min (&lt;34 breaths/min for neurologic injury)</td>
<td>After a period of stability PS is reduced by 2 cm H₂O</td>
</tr>
<tr>
<td></td>
<td>Vₜ &gt; 300 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P_{ETCO₂} &lt; 55 m Hg</td>
<td></td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>f &lt; 15 breaths/min</td>
<td>PS reduced by 4 cm H₂O</td>
</tr>
<tr>
<td></td>
<td>Vₜ &gt; 300 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P_{ETCO₂} &lt; 55 m Hg</td>
<td></td>
</tr>
<tr>
<td>Central hypoventilation</td>
<td>f &lt; 15 breaths/min</td>
<td>No change: may indicate a change to another mode of ventilation</td>
</tr>
<tr>
<td></td>
<td>Vₜ &lt; 300 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P_{ETCO₂} &lt; 55 m Hg</td>
<td></td>
</tr>
<tr>
<td>Unexplained hyperventilation</td>
<td>f &gt; 30 breaths/min</td>
<td>No change: may indicate a change to another mode of ventilation</td>
</tr>
<tr>
<td></td>
<td>Vₜ &gt; 300 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P_{ETCO₂} &lt; 20 m Hg</td>
<td></td>
</tr>
<tr>
<td>Tachypnea</td>
<td>f &gt; 30 breaths/min</td>
<td>Increase PS by 2 cm H₂O</td>
</tr>
<tr>
<td></td>
<td>Vₜ &gt; 300 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P_{ETCO₂} &gt; 20 but &lt; 55 m Hg</td>
<td></td>
</tr>
<tr>
<td>Severe tachypnea</td>
<td>f &gt; 36 breaths/min</td>
<td>Increase PS by 4 cm H₂O</td>
</tr>
<tr>
<td></td>
<td>Vₜ &gt; 300 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P_{ETCO₂} &gt; 20 but &lt; 55 m Hg</td>
<td></td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>f &lt; 15 breaths/min</td>
<td>Increase PS by 2 cm H₂O</td>
</tr>
<tr>
<td></td>
<td>Vₜ &gt; 300 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P_{ETCO₂} &gt; 55 m Hg</td>
<td></td>
</tr>
<tr>
<td>Insufficient ventilation</td>
<td>Normal Vₜ with elevated P_{ETCO₂}</td>
<td>Increase PS by 2 cm H₂O</td>
</tr>
<tr>
<td></td>
<td>f &gt; 15 breaths/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vₜ &gt; 300 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P_{ETCO₂} &gt; 55 m Hg</td>
<td></td>
</tr>
</tbody>
</table>
Low VT with normal $P_{ETCO_2}$
- $f > 15$ breaths/min
- $VT < 300$ mL
- $P_{ETCO_2} < 55$ m Hg

| Abbreviations | f = respiratory frequency; $P_{ETCO_2}$ = end tidal partial pressure of carbon dioxide; PS = Pressure support; VT = tidal volume. |


Rose and colleagues conducted a Cochrane systematic review and meta-analysis of automated versus non-automated weaning for reducing the duration of mechanical ventilation for critically ill adults and children. They identified 21 eligible trials that included 1,676 participants. The overall quality of evidence was high. Pooled data from 16 trials indicated that automated systems reduced the mean weaning duration by 30% (95% CI, 13%–45%), but with substantial heterogeneity. Reduced weaning duration of 43% (95% CI, 7%–49%) was found with mixed or medical ICU populations and Smartcare/PS, but not with surgical populations or other automated systems. Automated systems reduced ventilation duration (10%; 95% CI, 3%–16%) and ICU stay (8%; 95% CI, 0%–15%). There was no effect on mortality, hospital stay, reintubation, self-extubation, and NIV following extubation. Automated systems reduced prolonged mechanical ventilation and tracheostomy. The authors concluded that automated systems might reduce the duration of mechanical ventilation and ICU stay. Because of substantial trial heterogeneity, however, an adequately powered multicenter randomized controlled trial is needed. Because the safety of automated systems for young children has not been rigorously assessed, use in this population should be limited.

**EXTUBATION**

Extubation should be considered when the patient has successfully completed an SBT. Reintubation is associated with morbidity and mortality risk, but prolonged intubation in a patient who could be extubated is also associated with poorer outcomes. A reasonable reintubation rate is 10% to 20%. Before extubation, the clinical team (physicians, nurses, respiratory therapists) should agree to proceed with removal of the endotracheal tube, and a plan should be in place should extubation fail.

Before extubation, consideration should be given to the patient’s ability to clear secretions, neurologic status, and patency of the upper airway. Inability to perform four simple tasks by command or with stimulation (open eyes, follow with eyes, grasp hand, and stick out tongue), inability to generate a cough peak flow $>60$ L/min, and secretions $\geq 2.5$ mL/h have been reported to increase the risk of reintubation (Table 7). Cough peak flow and volume of secretions are not commonly quantified in the ICU. In a patient with a subjectively weak cough and a large volume of secretions (with the need for frequent suctioning), consideration should be given to delaying extubation; in some patients, tracheostomy might be reasonable to facilitate airway clearance. On the other hand, a patient with a weak cough but scant secretions might be able to be extubated successfully. The effect of neurologic function on airway protection is controversial. Some clinicians will proceed with extubation despite poor neurologic function, whereas others prefer tracheostomy. Many patients who are unable to follow commands but who have the ability to clear pulmonary
secretions can be safely extubated.  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Likelihood Ratio</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough peak flow ≤60 L/min</td>
<td>2.2</td>
<td>4.8 (1.4–16.2)</td>
</tr>
<tr>
<td>Secretions ≥2.5 mL/h</td>
<td>1.9</td>
<td>3.0 (1.01–8.8)</td>
</tr>
<tr>
<td>Unable to perform all 4 tasks (open eyes, follow with eyes, grasp hand, and stick out tongue)</td>
<td>4.5</td>
<td>4.3 (1.8–10.4)</td>
</tr>
<tr>
<td>Any 2 of the above risks</td>
<td>3.8</td>
<td>6.7 (2.3–19.3)</td>
</tr>
</tbody>
</table>


The potential for upper airway obstruction following extubation should always be considered before the tube is removed. Deflating the cuff and assessing for air leak around the tube when positive pressure is applied has been used to assess this. A lack of air movement around the tube suggests upper airway swelling and the potential for airway obstruction after removing the tube. The authors of a systematic review concluded that the absence of a leak (positive test) with the cuff leak test should alert the clinician to a high risk of upper airway obstruction. However, there are many false negatives, such as might occur with a large tube in a small trachea or secretions impacted above the cuff.

In one study, it was reported that failing the cuff leak test was not an accurate predictor of post-extubation stridor. The authors of this study concluded that the cuff leak test should not be used as an indication for either delaying extubation or initiating other specific therapy. Female patients, those whose ratio of endotracheal tube size to laryngeal diameter was > 45%, and those intubated for more than six days were more likely to develop post-extubation stridor. An issue with the cuff leak test is lack of a consistent definition; leak has been assessed subjectively (present or absent), as an absolute volume (>100 mL), or as a fraction of the inspired volume (>15.5%). However, it remains unclear whether the tidal volume or airway pressure should be standardized when cuff leak is measured.

Steroid therapy prior to extubation is indicated if upper airway swelling is suspected. This is supported by two meta-analyses that suggest that the incidence of post-extubation laryngeal edema is reduced if intravenously administered corticosteroids are started 12 to 24 hours before extubation and if multiple doses are administered. A study published after these meta-analyses supports the use of corticosteroids started four hours before extubation.

Evidence-base guidelines published in 2016 suggest performing a cuff leak test in mechanically ventilated adults who meet extubation criteria and are deemed high risk for post-extubation stridor. For adults who have failed a cuff leak test, but are otherwise ready for extubation, the same guidelines recommend administering systemic steroids for at least 4 hours before extubation.

**REDUCING RISK OF EXTUBATION FAILURE**
NIV can be used in the post-extubation period to shorten the length of invasive ventilation, to prevent extubation failure, and to rescue a failed extubation. NIV can be used to allow earlier extubation directly to NIV in selected patients who do not successfully complete an SBT, but its use in this setting should be restricted to patients who are intubated with COPD exacerbation, those with neuromuscular disease, and those who use NIV at baseline. Patients who successfully complete an SBT but who are at risk for extubation failure can be extubated directly to NIV to prevent extubation failure. Examples of patients at risk for extubation failure, who might benefit from extubation directly to NIV, are listed in Table 8. NIV should be used cautiously in patients who successfully complete an SBT but develop respiratory failure within 48 hours after extubation. In this setting, NIV is indicated only for patients with hypercapnic respiratory failure. Reintubation should not be delayed if NIV is not immediately successful in reversing post-extubation respiratory failure. Available evidence does not support routine use of NIV after extubation.

<table>
<thead>
<tr>
<th>TABLE 8. Patients at Risk for Extubation Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercapnia</td>
</tr>
<tr>
<td>Age &gt;65 years or &lt;1 year</td>
</tr>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Ineffective cough</td>
</tr>
<tr>
<td>Excessive tracheobronchial secretions</td>
</tr>
<tr>
<td>More than one failed spontaneous breathing trial</td>
</tr>
<tr>
<td>More than one comorbid condition</td>
</tr>
<tr>
<td>Partial upper airway obstruction</td>
</tr>
</tbody>
</table>

In recent years, the use of HFNC, with flows as high as 60 L/min in adolescents and adults, has become increasingly popular. Patients are traditionally extubated to face-mask oxygen or nasal cannula. Maggiore and colleagues conducted a randomized controlled trial of HFNC compared to an air entrainment mask after extubation. With HFNC, Pao$_2$/FiO$_2$ was higher, discomfort related to the interface and to airway dryness was better, fewer patients had interface displacements, oxygen desaturations were fewer, reintubation rate was lower, and any form of ventilator support was lower. These results provide limited support for the use of HFNC after extubation. Whether it should be used routinely or reserved for patients with hypoxemic respiratory failure has yet to be determined.

Mechanical insufflation-exsufflation (cough assist) uses positive inspiratory pressure and negative expiratory pressure to increase peak expiratory flow, thus simulating a cough. The cough assist device facilitates airway clearance in patients with neuromuscular weakness. Bach has shown that the use of NIV with aggressive use of cough assist can allow many patients with chronic neuromuscular disease to be extubated, sometimes even those with very low vital capacities. The use of cough assist has the potential to allow extubation of patients with a weak cough, although this needs further study in patients who do not have chronic neuromuscular disease.

KEY POINTS
Improvement in the underlying disease process, adequate gas exchange, minimal sedation, and hemodynamic stability are necessary before ventilator liberation.

Weaning parameters are poorly predictive.

The best way to determine ventilator liberation potential is the spontaneous breathing trial (SBT).

Synchronized intermittent mandatory ventilation should not be used for weaning in adult patients.

The SBT can be conducted in different ways and should be modified according to the patient’s baseline characteristics.

Providing too much support during the SBT may overestimate the chance of extubation success.

A failed SBT is often caused by an imbalance between the load on respiratory muscles and the capability of the muscles to meet that load.

In children, oversedation is a very common reason for a failed extubation trial.

Ventilator discontinuation protocols, when implemented correctly, can improve patient outcomes.

The role of automated systems to reduce the duration of mechanical ventilation has yet to be determined.

Noninvasive ventilation, high-flow nasal cannula, and cough assist are strategies that might decrease the risk of extubation failure in patients at risk.

REFERENCES

1. MacIntyre NR, Cook DJ, Ely EW Jr, et al; American College of Chest Physicians; American Association for Respiratory Care; American College of Critical Care Medicine. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest.* 2001 Dec;120(6 Suppl):375S-395S.


Chapter 10

THE ROLE OF RESCUE TREATMENTS FOR ARDS

Courtney M. Rowan, MD, Shira J. Gertz, MD, Robert F. Tamburro, MD, MSc, and Gregory A. Schmidt, MD

Objectives

- Identify clinical parameters that indicate a high likelihood of failure of conventional respiratory support
- Describe the most commonly implemented rescue therapies for patients with acute respiratory distress syndrome (ARDS) who fail conventional therapy
- Review the pertinent published literature regarding these therapies for both adult and pediatric populations
- Delineate the impact of these interventions on both gas exchange and patient-centered outcomes, recognizing that the former may not be an adequate surrogate of the latter
- To the extent possible, provide evidence-based recommendations for the use of these rescue strategies
- Offer potential topics and areas of needed knowledge for future research

INTRODUCTION

For most patients with acute respiratory distress syndrome (ARDS) or pediatric ARDS (PARDS), mechanical ventilation with lung-protective tidal volumes, positive end-expiratory pressure (PEEP), and treatment of the precipitating cause lead to improved gas exchange and ultimately recovery. More severely afflicted patients may benefit from prone ventilation, neuromuscular blockade (NMB), or higher PEEP levels. Yet some patients have profound gas exchange failure, including critical hypoxemia or hypercapnia, despite optimal conventional management. These failures of gas exchange may cause direct harm, including death, or provoke ventilator approaches, such as high fractions of inspired oxygen (FiO₂) or large driving pressures, that reduce the chances of lung recovery and survival.

Rescue therapies are devised to prevent death due to catastrophic gas exchange failure or to allow reductions in other noxious treatments in the hope of improving outcomes. Some treatments are based on the pathophysiology of ARDS, such as surfactant and inhaled vasodilators. Others, including NMB, prone ventilation, and inverse ratio ventilation (usually airway pressure release ventilation [APRV]), were recognized by astute clinicians to have beneficial effects on the arterial partial pressure of oxygen (Pao₂). Extracorporeal life support (ECLS) arose out of applications in the operating room, later adapted for use in the intensive care unit (ICU).

Determining the role that rescue therapies should play has been notoriously difficult. Patients with extreme lung failure are uncommon and clinically tenuous, rendering
them difficult to enroll in clinical trials. This is particularly true in pediatrics, given the relatively small and heterogeneous population of patients admitted to the ICU. Furthermore, some treatments considered for rescue, notably NMB and prone positioning, are considered adjuncts to lung protection based on an improved understanding of the ventilator’s role in amplifying lung injury. Demonstrating that these treatments improve outcome in broad groups of patients with moderate to severe ARDS does not necessarily inform us about their role as rescue therapies. In light of the challenges in obtaining high-quality data with respect to important outcomes such as survival, oxygenation responses have often been considered a surrogate for a beneficial effect. This understandable shortcut leads to the promulgation of approaches that have never been found to be beneficial on more patient-centered outcomes, including survival. Moreover, clinicians, who cannot treat sufficient numbers to draw statistically meaningful conclusions, may be so gratified by their patients’ oxygenation responses that their usual healthy skepticism is discarded.

In this chapter, we discuss commonly used rescue therapies for both adult and pediatric populations, delineating the impact of these interventions on both gas exchange and patient-centered outcomes, and offering evidence-based recommendations. We also describe an approach to integrate and prioritize the different treatments, including an evidence-based algorithm for adult ARDS (Figure 1).

**Figure 1.** Potential algorithm for treating refractory acute respiratory distress syndrome in adults

*Oxygen saturation < 88% with Fio$_2$ > 0.60 or Plateau pressure > 28 cmH$_2$O with Paco$_2$ > 45 mm Hg

- **NMB plus prone ventilation**
  - No improvement
  - **ECLS contraindication**
    - Yes
    - **Severe RV dysfunction**
      - No
      - Yes
      - APRV or permissive hypventilation
        - HFOV
  - **Transfer to ECLS-capable center**
    - Improvement
    - No improvement
    - **ECMO or ECCO$_2$R**
      - Improvement
      - Continue 48h -

*Despite customized PEEP and fluid-conservative management*

Abbreviations: APRV, airway pressure release ventilation; ECCO$_2$R, extracorporeal carbon dioxide removal; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; Fio$_2$, fraction of inspired oxygen; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; iPG, inhaled prostacyclin; NMB, neuromuscular blockade; Paco$_2$, partial arterial carbon dioxide pressure; PEEP,
positive end-expiratory pressure; RV, right ventricle.

**ADULT VIGNETTE**

A 33-year-old woman with obesity is admitted with acute hypoxemic respiratory failure. She had been in excellent health until two days ago when she had coryza, cough, headache, and chills, which progressed to profound dyspnea and confusion, leading to intubation and mechanical ventilation. A chest radiograph reveals diffuse, bilateral consolidation. Reverse transcriptase polymerase chain reaction testing confirms H1N1 influenza. Oseltamivir, 75 mg twice daily, is started enterally. A central venous catheter is inserted for measurement of central venous pressure (CVP), and diuresis is initiated, targeting a CVP < 4 mm Hg. She remains hemodynamically stable and displays normal renal function.

Ventilator settings are: volume assist control mode, tidal volume 6 mL/kg predicted body weight (PBW), respiratory rate (RR) 32 breaths/min, F\textsubscript{I\textsubscript{O}2} 0.5, and PEEP 18 cm H\textsubscript{2}O leading to a plateau airway pressure (Pplat) of 33 cm H\textsubscript{2}O. Arterial blood gas analysis reveals: Paco\textsubscript{2} 44 mm Hg and Pao\textsubscript{2} 58 mm Hg (Pao\textsubscript{2}/F\textsubscript{I\textsubscript{O}2} ratio [P/F] 116 mm Hg). She occasionally double-triggers the ventilator despite sedation.

A 15-mg bolus of cisatracurium is administered, followed by a continuous IV infusion at 37.5 mg/hr (**Table 1**). She is turned to the prone position, causing the Pplat to fall to 29 cm H\textsubscript{2}O and the P/F to rise to 132 mm Hg.

Despite these treatments, hypoxemia worsens over the next 24 hours (P/F 90 mm Hg), Pplat rises to 34 cm H\textsubscript{2}O on unchanged ventilator settings, and arterial carbon dioxide partial pressure (Paco\textsubscript{2}) is 47 mm Hg. She is turned supine in the operating room, and a 31-F dual-lumen cannula is inserted through the right internal jugular vein and placed across the right atrium. Extracorporeal membrane oxygenation (ECMO) is initiated, and she is returned to the ICU, where ventilator settings are changed to pressure assist control (PACV) mode, inspiratory pressure 20 cm H\textsubscript{2}O, expiratory pressure 10 cm H\textsubscript{2}O, F\textsubscript{I\textsubscript{O}2} 0.4, and RR 8 breaths/min, producing a tidal volume of 190 mL/kg.

Over the next 12 hours, she is stabilized on ECMO, cisatracurium is discontinued, and sedatives are withdrawn. When this is well tolerated, she is awakened and begins physical therapy. The next day, she is extubated and, while maintained on ECMO, is allowed to ambulate. Over the next 10 days, gas exchange and lung imaging demonstrate gradual improvement, leading to successful decannulation. After additional rehabilitation, she is discharged home on the 20th day, wearing 2 L/min oxygen by nasal cannula.

**TABLE 1.** Guidelines for the Use of Nonconventional and Adjunctive Therapies in the Treatment of Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Rescue Treatment</th>
<th>Adult</th>
<th>Pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFOV</td>
<td>MAP: 0–5 cm H\textsubscript{2}O above conventional MAP. Frequency: 5–12 Hz. Pressure amplitude: 90–100 cm H\textsubscript{2}O. Bias flow: 20 L/min.</td>
<td>MAP: 0–8 cm H\textsubscript{2}O above conventional MAP. Frequency: 5–15 Hz (decreasing with child’s size). Pressure amplitude: Chest wall vibration to the level of mid-thigh/pelvis.</td>
</tr>
<tr>
<td>NMB</td>
<td>Cisatracurium besylate, 15 mg IV bolus, then 37.5 mg/h for 48h.</td>
<td>Varies based on concurrent clinical condition, associated organ dysfunction, local preference, and drug availability.</td>
</tr>
<tr>
<td>APRV</td>
<td>( P_H: ) Equal to Pplat. ( P_L: ) 0 cm H(_2)O. ( T_H: ) 3.5–10 sec. ( T_L: ) 0.2–0.8 sec.</td>
<td>( P_H: ) Equal to Pplat. ( P_L: ) 0 cm H(_2)O. ( T_H: ) 4–6 sec. ( T_L: ) Time it takes for expiratory flow to fall to 25%–50% of peak expiratory flow.</td>
</tr>
<tr>
<td>INO</td>
<td>5–40 ppm.</td>
<td>5–40 ppm (usually ( \leq ) 20 ppm).</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Calfactant, 30 mg/cm (height) twice daily for 1–3 days. Divide dose, instill half in both right- and left-side down positions, directly into ETT.</td>
<td>Varies by preparation used.</td>
</tr>
<tr>
<td>Prone Ventilation</td>
<td>Ventilate prone 16+ hours/day.</td>
<td>Ventilate prone 16–20 hours/day.</td>
</tr>
<tr>
<td>ECMO</td>
<td>Mode: VV ECMO. Circuit flow: 3.5–6 L/min. Sweep gas flow: 1.5–15 L/min. Consider ultraprotective ventilation (( \leq 4 ) mL/kg) or extubation.</td>
<td>Mode: VV or VA ECMO. Circuit flow, VV: Start at 10–15 mL/kg/min and increase over 15 min to maximum of 150 mL/kg/min to achieve desired oxygenation. Circuit flow, VA: Start at 20 mL/kg/min, increase over 30 minutes to 100–120 mL/kg/min to achieve desired oxygenation/hemodynamic stability. Sweep gas: Start with 1:1 ratio with circuit flow and titrate as needed. Ventilator management: Consider PEEP 10–15 cm H(_2)O and minimizing Pplat &lt;30 cm H(_2)O, resulting in low tidal volumes.</td>
</tr>
<tr>
<td>ECCO(_2)R</td>
<td>Mode: VV ECLS or AV pumpless. Circuit flow 0.5–4 L/min. Sweep gas flow: 1–12 L/min. Consider ultraprotective ventilation (( \leq 4 ) mL/kg).</td>
<td>Not routinely used in pediatric population.</td>
</tr>
</tbody>
</table>

Abbreviations: APRV, airway pressure release ventilation; AV, arteriovenous; ECCO\(_2\)R, extracorporeal CO\(_2\) removal; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; ETT, endotracheal tube; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; MAP, mean airway pressure; NMB, neuromuscular blockade; Pplat, plateau airway pressure; VA, venoarterial; VV, venovenous.

**PEDIATRIC VIGNETTE**

An 18-month-old boy is admitted to the pediatric ICU (PICU) with progressive respiratory distress secondary to parainfluenza pneumonia. He requires intubation and invasive mechanical ventilation because of progressive hypoxemia, increased work of breathing, and an altered sensorium. Initially, the ventilator is set in pressure-regulated volume control (PRVC) mode with a tidal volume of 6 mL/kg PBW, \( F_{IO_2} \) 0.60, PEEP 6 cm H\(_2\)O, RR 20 breaths/min, and inspiratory time 1.0 second with a resultant Pplat 26 cm H\(_2\)O. Despite this support, he is unable to maintain an arterial oxygen saturation (Sao\(_2\)) > 80%, and his ventilator support is steadily advanced over the next 24 hours.

The next morning, in PACV mode, settings are: \( F_{IO_2} \) 0.65, PEEP 14 cm H\(_2\)O, inspiratory pressure 16 cm H\(_2\)O above PEEP, RR 20 breaths/min, and inspiratory time 1.2 seconds maintaining a tidal volume of approximately 6 mL/kg PBW. Arterial blood gas analysis reveals: pH 7.28, Paco\(_2\) 56 mm Hg, Pao\(_2\) 45 mm Hg, P/F 75 mm Hg and, with a mean airway pressure (MAP) of 20 cm H\(_2\)O, oxygenation index (OI) is
In addition to adequate sedation, he is receiving a continuous vecuronium infusion. A chest radiograph reveals worsening diffuse bilateral interstitial lung disease. An echocardiogram reveals elevated pulmonary vascular resistance and right ventricular strain. He is started on inhaled nitric oxide (iNO) at 20 ppm with a subsequent rise in $\text{Sao}_2$ from 79% to 84%, and an increase in $\text{Pao}_2$ to 51 mm Hg. He is placed prone, which causes a further increase in oxygenation; his $\text{Sao}_2$ rises to 90% and his $\text{Pao}_2$ to 58 mm Hg. His lung compliance also improves and his inspiratory pressure decreases to 12 cm H$_2$O while still maintaining the same tidal volume. He remains in the prone position for 16 hours with slow but steady increases in oxygen saturation.

After 16 hours, his $\text{Sao}_2$ is 89%, $\text{FiO}_2$ is weaned to 0.60, and he is returned to the supine position. His oxygenation and compliance deteriorate somewhat when in the supine position, and $\text{FiO}_2$ is transiently increased to maintain saturations in the mid-80s. After four hours, he is returned to the prone position. Given the high $\text{FiO}_2$ requirement and elevated ventilator pressures, high-frequency oscillatory ventilation (HFOV) is implemented. At this time, conventional ventilator was set in PACV mode with PEEP 14 cm H$_2$O, inspiratory pressure 18 cm H$_2$O above PEEP, $\text{FiO}_2$ 0.8, RR 20 breaths/min; his resultant tidal volume was only 5 mL/kg PBW. Initial HFOV settings are: MAP 28 cm H$_2$O (6 cm H$_2$O above the MAP on conventional ventilation), $\text{FiO}_2$ 1.0, amplitude 45, which provides a chest vibration down to the iliac crest, and frequency 10 Hz (Table 1). With initiation of HFOV, $\text{Sao}_2$ slowly rises and $\text{FiO}_2$ is gradually weaned. After 12 hours, $\text{Sao}_2$ ranges between 88% and 90%, and $\text{FiO}_2$ has been weaned to 0.70. Venovenous ECMO is considered, but given the steady, albeit slow, increase in oxygenation, a decision is made to continue with HFOV, barring acute deterioration. Eight hours later, oxygenation continues to improve, and $\text{FiO}_2$ has been weaned to 0.60. The other HFOV settings remain unchanged; arterial blood gas values reveal pH 7.30, $\text{Paco}_2$ 58 mm Hg, and $\text{Pao}_2$ 70 mm Hg. P/F is 117 mm Hg, and OI is 24. During the next several days, the patient remains on HFOV in the prone position for 16–20 hours a day and receives 20 ppm of iNO. His pulmonary status continues to improve, and HFOV support is steadily weaned.

By PICU day 10, HFOV support is reduced to MAP 18 cm H$_2$O, $\text{FiO}_2$ 0.5 and amplitude 36 cm H$_2$O, while the frequency remains at 10 Hz. He is transitioned to conventional ventilation in PRVC mode with PEEP 10 cm H$_2$O, tidal volume 6 mL/kg PBW, RR 16 breaths/min, and $\text{FiO}_2$ electively increased to 0.60. He does well with the transition and remains in this ventilator mode while NMB is discontinued, iNO weaned, and sedation reduced. Although he is doing adequately from a pulmonary standpoint, he is unable to be weaned off the ventilator because of profound neuromuscular weakness. Also, he is agitated during attempts to wean the IV sedation and transition to enteral medications. On PICU day 27, he receives a tracheostomy and is transferred to the rehabilitation unit.

**NEUROMUSCULAR BLOCKADE**

NMB is an effective tool to facilitate synchrony with mechanical ventilation, raise $\text{Pao}_2$, and decrease oxygen consumption. Most importantly, the results of the ACURASYS trial suggest that 48 hours of paralysis with cisatracurium may improve
survival in ARDS. Many intensivists have not embraced the implications of this study because mechanisms are uncertain, paralytics are judged as risky, clinicians have had good experiences with alternative modes such as APRV, or they believe that achieving synchrony with sedation and ventilator adjustment may be sufficient.

The two mechanisms that most likely explain any benefit of NMB are improved synchrony between patient and ventilator and the prevention of pendelluft. Many ARDS patients are asynchronous, often triggering the ventilator multiple times, and raising tidal volume over lung-protective limits. Paralysis prevents this effect, while deeper sedation does not. In addition, some patients activate expiratory muscles through end-expiration, countering the role of PEEP in recruiting lung and ameliorating atelectrauma. Thus, paralysis could serve to augment lung protection, thereby improving outcomes. Similar advantages might accrue by ensuring synchrony between patient and ventilator, but this is easy neither to achieve nor to assess.

Active inspiratory effort also produces pendelluft, a to-and-fro movement of gas between lung regions. In contrast to controlled ventilation with paralysis, which produces homogenous ventilation to dependent and nondependent lung zones, superimposed spontaneous breathing facilitates preferential ventilation of dependent lung zones early in the breath (at the expense of nondependent zones), effectively tripling the tidal volume locally. Such dependent overdistention in early inspiration may amplify local lung injury. This mechanism may not only explain the findings related to NMB, but also has implications for any mode of ventilation that allows spontaneous breathing, such as APRV.

NMB has been associated with ICU-acquired weakness, the risk of which may be amplified in patients who concurrently take corticosteroids and aminoglycosides, or have acute kidney injury. Monitoring the depth of paralysis using train-of-four stimulation has been advocated to reduce the risk of weakness, but this has never been found effective. Moreover, because the ACURASYS trial gave a fixed infusion of cisatracurium, the benefits demonstrated might not be produced with a lower dose. In patients with a known seizure disorder or those likely to seize (eg, head trauma), continuous EEG monitoring should be considered while using NMB because seizures may be masked. Additionally, in children, the potential for adverse effects on the developing brain and neuromusculature must be considered.

**Adult Data**

The effects of NMB on pulmonary and systemic inflammation in patients with moderate to severe ARDS (P/F ≤ 200 mm Hg) were first reported in a small, multicenter trial in a mixed medical-surgical population. All subjects were sedated to a Ramsay score of 6 (no response to glabellar tap) and ventilated in a manner similar to those in the ARDS Network low tidal volume trial, including volume assist control mode, tidal volume 6 mL/kg PBW, and Pplat below 30 cm H₂O. Those in the intervention arm also received cisatracurium for 48 hours titrated to no response on train-of-four stimulation at the orbicularis oculi muscle. Bronchoalveolar lavage and blood samples obtained at study entry and after 48 hours found that cisatracurium lowered the levels of interleukin (IL)-1β, IL-6, and IL-8. These results are intriguing because NMBs have no known direct anti-inflammatory response. Instead, their effect may be mediated through the mechanisms of synchrony or pendelluft.
In a subsequent trial, 340 adults with early, moderate to severe ARDS were randomized to conventional lung-protective ventilation with or without 48 hours of cisatracurium. Train-of-four monitoring was not used, and cisatracurium was given at a fixed dose. Patients receiving cisatracurium had lower mortality with a hazard ratio for death at 90 days of 0.68 (p = 0.04). In addition, intervention subjects spent more time alive and free of mechanical ventilation, were less likely to suffer barotrauma, and did not experience more ICU-acquired weakness.

**Pediatric Data**

There is a paucity of pediatric data regarding the use of NMB in respiratory failure. One retrospective cohort study of 317 mechanically ventilated children compared patients who received NMB (n = 34) for at least 12 hours with control subjects who did not. Children who received NMB had significantly longer durations of mechanical ventilation (13.7 vs. 5.5 days, p < 0.0001), longer lengths of PICU stay (20 vs. 11 days, p < 0.0001), and higher rates of ventilator-associated pneumonia (6.6 vs. 4.1 per 1,000 ventilated days, p = 0.01). Although there was no significant difference in mortality, children who received NMB had a twofold lesser mortality rate than children who did not (8.8% vs. 17.7%, p = 0.29).

**Recommendations**

For most adult patients with moderate to severe ARDS (P/F < 150 mm Hg following adequate sedation), we advocate infusing cisatracurium at a dose of 37.5 mg/hr for 48 hours following a loading bolus of 15 mg, and not monitoring the degree of paralysis. For pediatric patients with PARDS, NMB is recommended in respiratory failure only when sedation alone cannot achieve effective and safe mechanical ventilation. Children should receive the minimal effective dose to minimize potential toxicity.

**Additional Areas for Research**

The adult intensivist community has not fully embraced the role of NMB because of uncertain mechanisms, potential risks, and reliance on a single clinical trial. Additional study is warranted to corroborate these findings, more carefully assess neuromuscular and functional outcomes, and establish the biological basis for any benefit. Given the encouraging findings among adults, more research among children is also needed. One pediatric study suggests a survival advantage for NMB despite discouraging short-term outcome results. Further research should report the goal, strategy, and exposure of NMB, as well as the monitoring techniques and outcomes, to allow for comparisons across studies. Given the potential toxicities of NMB, long-term parameters of physical and psychological well-being should be measured, as well as developmental outcomes.

**PRONE POSITIONING**

Prone ventilation for ARDS is being used more widely after a large trial demonstrated that it reduced mortality in adults with moderate to severe disease. CT scanning of
patients with ARDS typically reveals large zones of dependent atelectasis that contribute to intrapulmonary shunt. Prone positioning increases ventilation to well-perfused zones of the dorsal lung, thereby reducing intrapulmonary shunt and raising $P_{aO_2}$. Proning ARDS patients raises $P_{aO_2}$ roughly two-thirds of the time, often dramatically, so this approach has a time-tested place in the intensivist’s armamentarium for treating critical hypoxemia. Recent data suggest, however, that augmentation of oxygenation probably does not account for the benefit of prone positioning. More likely mechanisms involve the enhanced homogeneous distribution of end-expired lung volume or the unloading of the right ventricle. When ventilated in the supine position, ARDS patients have some lung zones that are atelectatic despite PEEP, while other areas are overdistended. Proning simultaneously reduces the proportion of non-aerated lung and the overdistended lung. In this regard, proning should be considered more as a tool for lung protection than as a means to raise $P_{aO_2}$. Prone ventilation also reduces pulmonary artery pressures and, in the subset of patients with impaired cardiac output due to acute cor pulmonale, augments systemic perfusion.

Prone positioning involves placing the patient facedown, carefully avoiding excessive pressure on the eyes, nose, and other prominences. Such positioning has the potential to complicate care because it limits access to endotracheal tubes, central lines, urinary catheters, and the sternum if there is a need for cardiopulmonary resuscitation (although it can be performed in the prone position). Infants are relatively easy to prone because of their small size. Turning larger patients requires a team approach, with care taken to protect the endotracheal tube, vascular catheters, monitoring equipment, and other support devices. Occasional serious complications have been described. In a meta-analysis, prone ventilation raised the risk of pressure ulcers, endotracheal tube occlusion, and chest tube dislodgement. Nevertheless, prone ventilation can be conducted safely in both pediatric and adult populations.

**Adult Data**

Several early trials found that prone positioning could raise $P_{aO_2}$ but had no apparent effect on survival. These studies were often underpowered, not conducted in the era of lung-protective ventilation, enrolled mild to severe ARDS patients, or mandated the prone position for only a few hours per day. Meta-analyses pointed to a potential role, especially in the most severe patients, and found an overall favorable risk profile.

A recent landmark trial, PROSEVA, involving 466 subjects, demonstrated that, combined with lung-protective ventilation, early and prolonged prone positioning improved survival of ARDS patients with $P/F < 150$ mm Hg. Subjects were enrolled within 36 hours of onset and were placed in the prone position for at least 16 hours each day. Prone treatment continued for up to 28 days, or until oxygenation improved ($P/F \geq 150$ mm Hg four hours after returning to the supine position while on $F_{O_2} \leq 0.6$ and $PEEP \leq 10$ cm H$_2$O), or if proning produced complications or a deterioration in oxygenation. The average number of proning sessions was four, and 73% of the time ventilation was in the prone position. All ICUs were experienced with prone treatment, and a protocol for safe proning was provided, calling for three to four team members for turning. Knees, forehead, chest, and iliac crests were padded. Patients were prone in the horizontal position; no special beds or proning...
devices were used.

The P/F ratio was higher in prone subjects, while both FiO₂ and PEEP were lower. Mortality was significantly lower in the prone group at 28 days (16 vs. 33%; \(p < 0.001\)); this persisted at 90 days (24 vs. 41%; \(p < 0.001\)). Prone treatment also shortened ICU length of stay, reduced the rate of rescue therapies (eg, iNO, ECMO), and increased ventilator-free days. There was no difference in the rate of complications, including endotracheal tube malposition, except that cardiac arrest was more common in the supine group. These results support the use of prone ventilation for adults with moderately severe ARDS.

**Pediatric Data**

In the early 2000s, single-center studies demonstrated that prone positioning could be safely performed in pediatric patients with no critical adverse events or persistent decreases in oxygenation (Table 2). In both retrospective and prospective studies, patients experienced increased oxygenation with prone positioning. As a result, a multicenter, randomized controlled trial was conducted in which 102 children were randomized to prone or supine positions. Patients in the prone arm were prone within four hours of randomization and remained so for 20 hours each day. Ninety percent of the patients in the prone arm were considered responders. However, the study was halted at the planned interim analysis on the basis of futility. Although proning was found to be safe, no differences were detected between the two treatment arms in terms of ventilator-free days (the primary study outcome), all-cause mortality, time to recovery from lung injury, number of organ failure-free days, cognitive function, or overall health. These studies suggest that prone positioning in PARDS is relatively safe and may be associated with increased oxygenation, but there seems to be no benefit in any other outcomes measured.

### Table 2: Studies Assessing Prone Positioning in Children with Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Increased Oxygenation</th>
<th>Mortality</th>
<th>Outcomes</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murdoch 1994</td>
<td>Single-center case series N = 7</td>
<td>Yes</td>
<td>No difference</td>
<td>Improved oxygen delivery.</td>
<td>Prone position maintained for only 30 minutes.</td>
</tr>
<tr>
<td>Curley 1999</td>
<td>Systematic review N = 297</td>
<td>Yes</td>
<td>No difference</td>
<td>Cumulative and persistent increases in oxygenation.</td>
<td>Rare adverse events.</td>
</tr>
<tr>
<td>Curley 2000</td>
<td>Single-center case series N = 25</td>
<td>Yes</td>
<td>No deaths</td>
<td>84% of patients had oxygenation improvement.</td>
<td>No patient had a critical incident or decrease in oxygenation.</td>
</tr>
<tr>
<td>Kornecki 2001</td>
<td>Single-center RCT with crossover N = 10</td>
<td>Yes</td>
<td>No deaths</td>
<td>Improved oxygenation.</td>
<td>No serious adverse events.</td>
</tr>
<tr>
<td>Bruno 2001</td>
<td>Single-center case series N = 10</td>
<td>Five (28%) patients had increased oxygenation.</td>
<td>No deaths</td>
<td>28% of patients had improved oxygenation after one hour of prone positioning.</td>
<td>No serious adverse events.</td>
</tr>
<tr>
<td>Casado-Flores 2002</td>
<td>Single-center case series N = 23</td>
<td>Yes</td>
<td>39% of responders vs. 80% of non-responders</td>
<td>Patients fell into responder and non-responder groups.</td>
<td>Due to small sample size, results did not achieve statistical significance.</td>
</tr>
<tr>
<td>Study</td>
<td>Design Type</td>
<td>N</td>
<td>Outcome</td>
<td>Effect on Ventilator-Free Days</td>
<td>No Change</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>-----</td>
<td>---------</td>
<td>-------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Relvas 2003</td>
<td>Single-center retrospective chart review</td>
<td>40</td>
<td>Yes</td>
<td>No difference</td>
<td>Yes</td>
</tr>
<tr>
<td>Lopez-Herce Cid 2003</td>
<td>Single-center case series</td>
<td>18</td>
<td>Yes</td>
<td>No difference</td>
<td>Yes</td>
</tr>
<tr>
<td>Curley 2005</td>
<td>Multicenter RCT</td>
<td>102</td>
<td>Yes</td>
<td>No difference</td>
<td>Yes</td>
</tr>
<tr>
<td>Sud 2008</td>
<td>Meta-analysis: 13 studies published between 1997–2007</td>
<td>1,559</td>
<td>Yes</td>
<td>No difference</td>
<td>Yes</td>
</tr>
<tr>
<td>Sud 2010</td>
<td>Meta-analysis: 10 studies published between 2001–2009</td>
<td>1,867</td>
<td>Yes</td>
<td>Reduced in those with severe hypoxia.</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: iNO, inhaled nitric oxide; MAP, mean airway pressure; OI, oxygenation index; P/F, Pao2/Fio2 ratio; RCT, randomized, controlled trial.

The subset of patients with severe hypoxemia, however, may merit further scrutiny. In 2008, Sud and colleagues published a meta-analysis that included children, which demonstrated no changes in mortality with prone positioning, but sustained improvement in the ability to oxygenate. In a subsequent meta-analysis that also included both adult and pediatric patients, the same investigators reported an association between prone positioning and decreased mortality among patients with profound hypoxemia (P/F < 100 mm Hg). The PROSEVA trial also demonstrated a significant survival benefit of prone positioning in adults with at least moderately severe ARDS (P/F < 150 mm Hg). These data support further investigation in children with severe hypoxemia.

**Recommendations**

In light of the data in adults, we advocate prone ventilation for lung protection in adults with P/F < 150 mm Hg. For patients with more critical degrees of hypoxemia, we recommend initiating or continuing proning. In light of available pediatric data, proning cannot be recommended as routine therapy for PARDS. However, it may be considered with severe refractory hypoxic respiratory failure that is unresponsive to other measures.

**Additional Areas for Research**

In clinical trials, many subjects received both prone ventilation and NMB, potentially
confounding their respective roles and making it uncertain whether both therapies are indicated simultaneously. Further study should better delineate these effects and perhaps assess for a synergistic benefit. Pediatric studies should investigate whether the mechanisms of lung protection demonstrated in adults pertain to children. Also, because of the adult studies that demonstrated a survival benefit and the results of published meta-analyses, additional study should focus on children with severe ARDS.

**AIRWAY PRESSURE RELEASE VENTILATION**

APRV is used as a rescue therapy in ARDS, particularly for severe cases. APRV applies a high airway pressure during most of the respiratory cycle, with short periods when the airway pressure is reduced to zero or low values. It is a form of inverse ratio ventilation that facilitates spontaneous breathing during both high- and low-pressure periods. High, continuously applied airway pressure can both maintain lung volume and recruit additional alveoli at lower peak inspiratory pressures than conventional mechanical ventilation. In addition, the very short expiratory time produces auto-PEEP. Proponents of APRV cite improved patient comfort, less need for sedation and NMB, and improved hemodynamic stability.

Empirically, APRV can raise Pao$_2$ in patients with refractory hypoxemia. This may be a seductive finding, however—it may be analogous to the higher Pao$_2$ that attends high tidal volume ventilation, yet is associated with poor outcomes. Concerns with APRV include tidal volumes (equivalently “driving pressure”) that are often higher than would be considered lung protective and the potential for derecruitment (and atelectrauma) during periods when airway pressure is lowered. Also, if spontaneous effort is harmful in early, severe ARDS, APRV may be counterproductive.

**Adult Data**

There are no high-quality data comparing APRV with conventional lung-protective ventilation for patients with ARDS, despite 30 years of use. In an observational study of ARDS patients, APRV was associated with a lesser degree of sedation and lower sedative doses when compared with those managed with assist control ventilation. Hemodynamic effects of APRV, when compared with pressure support mode, include higher cardiac output and right ventricular ejection fraction, probably related to the lower pleural pressure attending spontaneous effort combined with the pulmonary vascular effects of enhanced lung recruitment. A case-matched, secondary analysis of a multicountry observational study revealed no differences between APRV and volume assist control ventilation with regard to days of ventilation, ICU or hospital length of stay, or mortality. However, in a retrospective analysis of a trauma population, APRV appeared to increase ventilation time after controlling for potential confounding factors using a multiple regression model.

APRV was compared with synchronized, intermittent, mandatory ventilation (SIMV) in a prospective trial, but no impact was found on ventilator-free days or mortality. Moreover, the SIMV arm did not receive conventional lung-protective ventilation. Finally, in a study of trauma patients randomized to APRV or a low-tidal volume conventional approach, APRV use was associated with a trend toward increased ventilator days, ICU length of stay, and ventilator-associated pneumonia. These findings might be explained by the somewhat higher illness severity (despite
randomization) of the APRV subjects. Nevertheless, taken together, all of these data suggest little reason to prefer APRV over conventional ventilation.

**Pediatric Data**

The pediatric data are relatively scant and limited mostly to observational studies. Very few data demonstrate appropriate settings or the best approach to transition to and from conventional mechanical ventilation. In one pediatric crossover study of 15 patients treated with either APRV or conventional mechanical ventilation, nine patients were started on conventional ventilation and six on APRV. Patients were crossed over to the other mode at the time of enrollment. APRV was found to be as effective in gas exchange, patient comfort, and hemodynamic stability as conventional ventilation. However, only patients with mild to moderate lung disease were included in the study. APRV was also associated with lower Pplats (18 ± 6 vs. 23 ± 8 cm H\textsubscript{2}O, \( p \leq 0.005 \)), yet transpulmonary pressure, the likely more relevant pressure, was not lower with APRV. Other studies in the pediatric population consist primarily of case series suggesting that APRV can be safely applied in pediatric patients and that it increases oxygenation.

**Recommendations**

APRV is used widely for severe ARDS in adults, but its use is based largely on its impact on oxygenation or a preference to sustain spontaneous breathing and reduce sedation; these goals are suspect. We recommend that APRV be used under the auspices of a clinical trial or only when more established alternatives (ECMO, NMB, prone ventilation) are unavailable or ineffective. In the pediatric population, there is insufficient data to recommend for or against APRV. Existing data demonstrate that it can be safely used in the pediatric population; it holds the potential to increase oxygen levels.

**Additional Areas for Research**

Prospective, interventional trials comparing APRV to other forms of lung-protective ventilation are needed to better understand its utility in adult and pediatric populations. A rationale for specific settings should be provided and codified into protocols. These trials should report measures such as tidal volume and should focus on patient-centered outcomes such as ventilator-free days, ICU length of stay, and survival, rather than gas exchange. Specific protocols for transitioning to and from APRV, details regarding sedation, NMB, vasoactive infusions, and potential complications such as pneumothoraces, should be reported. APRV should also be compared to HFOV because no existing data demonstrate superiority of one mode over the other.

**HIGH-FREQUENCY OSCILLATORY VENTILATION**

HFOV is an alternative mode of ventilation in which the MAP is maintained constant while an oscillating pump delivers small (often less than dead space) tidal volumes at a rapid rate. HFOV has drawn interest in the management of ARDS for two reasons: First, it is the logical extension of the open-lung approach to lung-protective ventilation by virtue of maintaining high MAP (to keep the lungs open) while superimposing only very small tidal swings (to keep driving pressure and tidal
volumes small). Second, the high MAP characteristic of HFOV has the potential to recruit lung alveolar units when PEEP is ineffective, thereby raising \( \text{Pao}_2 \) in ARDS patients with critical and refractory hypoxemia.

Gas exchange in HFOV occurs through the direct ventilation of proximal alveoli, Taylor dispersion, convection, pendelluft, collateral ventilation, and diffusion (Figure 2). With regard to \( \text{CO}_2 \) exchange, HFOV is less efficient than conventional ventilation, such that \( \text{Paco}_2 \) typically rises when patients are converted to HFOV, despite higher airway pressures. For example, in one prospective trial of adults with ARDS, \( \text{Paco}_2 \) was approximately 6 mm Hg higher in the HFOV subjects than in those ventilated conventionally, despite MAPs 3–4 cm H\(_2\)O higher.\(^9\)

**Figure 2.** Proposed mechanisms of gas exchange in high-frequency oscillatory ventilation


In HFOV, the main ventilator settings are: MAP, amplitude of the oscillatory pressure, frequency (Hz), bias flow, \( \text{FiO}_2 \), and inspiratory time. Each exerts a unique effect that influences the patient’s overall oxygenation and ventilation. For example, MAP is the primary setting that regulates lung volume and alveolar recruitment so that, in conjunction with \( \text{FiO}_2 \), it exerts the most control over oxygenation. Amplitude determines the displacement of the piston in the ventilator; this displacement impacts the volume delivered to the patient (oscillatory volume). Empirically, the \( \text{Paco}_2 \) level
correlates inversely with the product of the frequency and the square of the oscillatory volume. Because oscillatory volume (unlike tidal volume during conventional ventilation) is a complex function of amplitude, frequency, and duty cycle, the impact of ventilator changes on gas exchange is not self-evident. For example, reducing frequency tends to lower Paco\textsubscript{2} because oscillatory volume rises as a consequence, and this secondary effect has a greater impact on CO\textsubscript{2} exchange than the lower respiratory rate.

HFOV has hemodynamic effects that must be considered as well. The higher MAP, combined with the impact of alveolar recruitment, raises pleural and juxtacardiac pressure, potentially limiting cardiac filling. In one trial of HFOV, the net fluid balance was higher in the HFOV group (although the difference was not significant),\textsuperscript{10} and yet HFOV subjects were more likely to be treated with vasoactive medications, and these medications were administered for an average of two days longer. Transesophageal echocardiography reveals that HFOV also impairs right ventricular systolic function more than conventional ventilation, the degree of impairment rising along with the MAP.

**Adult Data**

Early studies of ARDS included small numbers of subjects, or failed to use protective ventilation in the control arm, thereby limiting conclusions about efficacy or safety. Two recent, large, prospective, randomized trials compared HFOV to conventional lung-protective ventilation in adults.\textsuperscript{9,10} In the first, OSCAR, 795 patients were randomized to HFOV (initial settings were MAP 5 cm H\textsubscript{2}O above the MAP at enrollment, frequency 10 Hz) or conventional ventilation (local usual practice, although PACV and tidal volume 6–8 mL/kg PBW were encouraged). There was no difference in all-cause mortality 30 days after randomization (the primary outcome), days on vasoactive drug infusions, or hospital or ICU length of stay. Values for Pao\textsubscript{2} and Paco\textsubscript{2} were higher in the HFOV group (P/F 192 vs. 154 mm Hg, Paco\textsubscript{2} 55 vs. 50 mm Hg, respectively, on day 1) and NMB was more likely to be used initially in these patients. Vasoactive drugs were used in similar proportions in both groups.

In the second trial, OSCILLATE, 548 subjects were randomized to HFOV (initial MAP 30 cm H\textsubscript{2}O, adjusted to oxygenation; frequency 3–12 Hz) or conventional ventilation (PACV, tidal volume 6 mL/kg PBW; high PEEP table).\textsuperscript{10} Values for Pao\textsubscript{2} were similar (P/F 135 vs. 147 mm Hg for HFOV and conventional ventilation, respectively), while Paco\textsubscript{2} was lower with HFOV (46 vs. 52 mm Hg on day 1). Those treated with HFOV received higher sedative doses and were more likely to be given NMB. In-hospital mortality was significantly higher in the HFOV group (47 vs. 35%; \( p = 0.005 \)), causing the study to be terminated early.

**Pediatric Data**

In the pediatric intensive care community, HFOV has gained widespread popularity despite limited data supporting its use. In the neonatal population, its use is supported by evidence; however, the etiology of lung disease in neonates is much different than that of older children. While some of the neonatal data may be applicable to pediatric intensive care, in this section, we will discuss only literature specific to the non-neonatal pediatric population.
HFOV has been supported as a rescue therapy in PARDS by a reasonable amount of data suggesting it raises Pao\(_2\). In 1994, a five-center, randomized controlled trial of HFOV versus conventional ventilation was conducted in 70 pediatric patients with acute lung injury or air leak syndrome.\(^{11}\) In that trial, the use of HFOV was associated with raised oxygenation evidenced by a decreasing OI and less need for supplemental oxygen at day 30 (odds ratio 5.4, 95% CI: 1.2–23.2, \(p = 0.039\)). However, there was no difference between the two ventilator approaches in many outcomes, including ventilation duration and survival. It is important to recognize that this study was completed before the advent of low tidal volume strategies, and therefore the conventional arm is not a true representation of current therapy. More recent pediatric data demonstrate similar oxygenation results and have a variety of limitations. For example, there have been several observational and post hoc analyses demonstrating higher Pao\(_2\) (Table 3), but the vast majority of studies demonstrate no difference in mortality between HFOV and conventional mechanical ventilation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
<th>Increased Oxygenation</th>
<th>Mortality</th>
<th>Outcomes</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold 1994</td>
<td>Multicenter RCT (N = 70)</td>
<td>Yes</td>
<td>No difference</td>
<td>No difference in ventilation duration or length of stay.</td>
<td>Less supplemental oxygen at 30 days. Prior to low tidal volume ventilation strategy era.</td>
</tr>
<tr>
<td>Sarnaik 1996</td>
<td>Single-center observational (N = 31)</td>
<td>Yes</td>
<td>26% overall mortality</td>
<td>No comparison.</td>
<td>Lower starting OI and &gt; 20% improvement in OI at 6 hours associated with survival.</td>
</tr>
<tr>
<td>Brogan 2000</td>
<td>Single-center observational (N = 66)</td>
<td>Yes</td>
<td>59% overall mortality</td>
<td>No comparison.</td>
<td>Oxygenation improvement sustained only for patients with isolated respiratory failure.</td>
</tr>
<tr>
<td>Dobyns 2002</td>
<td>Multicenter post hoc analysis of RCT on use of iNO in severe AHRF (N = 108) (26 treated with HFOV)</td>
<td>Yes</td>
<td>No difference</td>
<td>No difference in mortality among any of the 4 groups (CMV alone, CMV + iNO, HFOV alone, HFOV + iNO).</td>
<td>HFOV with iNO had greatest improvement in oxygenation. At 72 hours, HFOV improved P/F more than either CMV arm.</td>
</tr>
<tr>
<td>Slee-Wijffels 2005</td>
<td>Single-center observational (N = 53) (one patient excluded from analysis)</td>
<td>Yes</td>
<td>36% overall mortality</td>
<td>No comparison.</td>
<td>Suggest early intervention with HFOV may be beneficial.</td>
</tr>
<tr>
<td>Ben Jaballah 2006</td>
<td>Single-center observational (N = 20)</td>
<td>Yes</td>
<td>25% overall mortality</td>
<td>No comparison.</td>
<td>Target ventilation achieved in all patients. 19 (95%) had improved oxygenation.</td>
</tr>
<tr>
<td>Fioretto 2011</td>
<td>Single-center RCT with crossover (N = 28)</td>
<td>Yes</td>
<td>No difference</td>
<td>HFOV caused earlier Fi(_O_2) reduction and increased P/F compared to CMV.</td>
<td>Oxygenation improvement not sustained.</td>
</tr>
<tr>
<td>Greathouse 2012</td>
<td>Single-center retrospective observational (N = 23)</td>
<td>Yes</td>
<td>29%</td>
<td>No comparison.</td>
<td>Exclusively pediatric burn patients. Earlier HFOV associated with less barotrauma.</td>
</tr>
<tr>
<td>Li 2013</td>
<td>Single-center retrospective observational (N = 64)</td>
<td>Yes</td>
<td>39%</td>
<td>No comparison.</td>
<td>Exclusively pediatric post-cardiac surgery patients. One-third developed pneumothorax.</td>
</tr>
</tbody>
</table>
An observational study described 66 children treated with HFOV and found higher Pao$_2$ over the first 72 hours of treatment; however, this increase was not sustained in children with multiorgan system dysfunction. Patients with primary lung disease were much more likely to experience increased oxygen levels with HFOV compared to other cohorts (relative risk 2.5, 95% CI: 1.5, 4.2). While overall mortality in this study was 59%, only 12% of those with isolated respiratory failure died. Conversely, children with primary cardiac disease were less likely to respond to HFOV (relative risk 0.3, 95% CI: 0.1, 0.8). Another observational study of 52 pediatric patients receiving HFOV also demonstrated higher Pao$_2$ with HFOV. This study also suggested that earlier intervention may be associated with improved survival in diffuse alveolar lung disease, as the survivors’ median OI at HFOV initiation was 10 points lower than the nonsurvivors ($p < 0.05$). Another small, prospective, observational study from 2006 reported that HFOV resulted in higher oxygenation and a decrease in ventilator support. Overall mortality was 25%. However, interpretation of this study is difficult due to its small sample size ($n = 20$) and exclusion of some patients with the late use of HFOV or obstructive lung disease.

Two additional studies assessing the combined use of iNO and HFOV found that HFOV raised Pao$_2$. In a 2002 post hoc analysis of a multicenter randomized controlled trial of iNO, HFOV, with or without iNO, raised Pao$_2$ over the first 72 hours. More recently, Fioretto conducted a prospective, randomized crossover study of HFOV and conventional mechanical ventilation among 28 children. The
children who started the trial receiving HFOV had a higher P/F at 8 hours, but this was not sustained at 24 hours. There was no difference in mortality between HFOV and conventional ventilation in either of these studies.

While data seem to clearly support that HFOV acutely raises oxygenation, when more long-term outcomes such as mortality and length of stay are assessed, the results are mixed. As with other rescue therapies, this emphasizes that increased oxygenation may not serve as an adequate surrogate for meaningful benefit. Studies assessing the length of PICU stay or ventilation duration have demonstrated either no difference or longer courses with HFOV. Additionally, a relatively recent retrospective review of 104 children receiving either APRV or HFOV found that children on HFOV had a greater need for iNO and NMB at 72 hours. There was also a trend toward increased vasopressor use with HFOV, although this study lacked a true control group; no patients received conventional ventilation. Gupta and colleagues recently published a retrospective, observational, matched severity-of-illness comparison using patients from the Virtual PICU System database. A total of 9,177 patients were identified, of whom 902 received HFOV. The patients receiving HFOV were matched with conventional ventilation controls based on demographics and clinical characteristics, which included severity of illness at admission. Although the study demonstrated raised oxygenation with HFOV, mortality in the HFOV cohort was more than double that of the conventional mechanical ventilation group (17.3% vs. 8.4%, respectively, p < 0.001). There was also a longer length of PICU stay (24.9 vs. 19.1 days, p < 0.001) and a longer course of mechanical ventilation (20.3 vs. 14.6 days, p < 0.001) in those treated with HFOV. The report suggested that even early intervention with HFOV was not superior to conventional mechanical ventilation. Limitations of this study include the use of a matching propensity score that did not effectively assess acute hypoxemia and the inability to compare the severity of hypoxemia at baseline between the two groups. Consequently, caution is advised in drawing definitive conclusions.

Most recently, Bateman and colleagues published a post hoc analysis of HFOV use in the multicenter RESTORE trial. They compared the early initiation (within 48 hours of intubation) of HFOV with late HFOV or conventional mechanical ventilation. Of 2,449 patients, 210 were treated with early HFOV. Propensity scoring, which included the degree of hypoxia as the most important contributor to the model, was used to adjust both mortality and duration of mechanical ventilation comparisons between children receiving early HFOV and those receiving late HFOV or conventional mechanical ventilation. The analysis identified no difference in mortality, but HFOV was associated with a longer course of mechanical ventilation and an increased need for sedation and NMB.

Studies in unique pediatric populations, including burn patients, post-cardiac surgery patients, and immunocompromised patients, have also found increases in oxygenation, but all have been observational studies without a comparison group. Although the mortality reported in these studies seems to be consistent with that reported for these populations in other studies, it is difficult to draw any definitive conclusions regarding the value of HFOV for these specialized pediatric populations without a control group.

**Recommendations**
We agree with the recommendations of the OSCAR and OSCILLATE investigators that HFOV should not be used routinely in adults. It is important to consider, however, that both of these studies address whether HFOV confers superior lung protection when used in moderate to severe ARDS, and not whether HFOV has a role as a rescue therapy. At least when used according to the methods in these trials, conventional low-tidal volume ventilation is at least as good as HFOV, and perhaps superior, with regard to lung protection. Indeed, these results have called into question our theories about the nature of ventilator-induced lung injury and how best to protect the lung.

There are few data from which to judge the role of HFOV to rescue the severely hypoxemic patient. In the OSCILLATE trial, fewer HFOV patients had refractory hypoxemia (7% vs. 14%; \( p = 0.007 \); refractory defined as \( \text{Pao}_2 < 60 \text{ mm Hg} \) for 1 hour with \( \text{FiO}_2 1.0 \) and following NMB) although similar proportions of these patients died subsequently (79 vs. 66%). Inferring the role of HFOV as rescue is further complicated by uncertainties regarding the levels of \( \text{Pao}_2 \) that can be safely tolerated, and for how long, as well as by the complexities of the impact of HFOV on \( \text{Paco}_2, \text{pH} \), and cardiopulmonary interactions. If HFOV is chosen as rescue therapy for adults with refractory hypoxemia, careful and serial assessment of fluid balance and right ventricular function is recommended.

In the treatment of PARDS, a role for HFOV is not well established. Moreover, growing concerns regarding increased ventilation duration, increased length of stay, and greater need for sedation and NMB call into question its utility for non-neonatal pediatric patients. With the paucity of controlled, prospective data, we cannot recommend for or against the use of HFOV in the pediatric population with PARDS. Recommendations from the recent Pediatric Acute Lung Injury Consensus Conference (PALICC) suggest that it is reasonable to consider HFOV in moderate to severe hypoxic respiratory failure in children with Pplat exceeding 28 cm H\(_2\)O.

**Additional Areas for Research**

Our current understanding of lung protection supports a role for HFOV; thus, the recent negative trials raise concern that specific methodologic limitations, rather than conceptual flaws, are to blame. Therefore, additional basic study of lung-protective mechanisms and further trials of improved methods for delivering HFOV could be championed. Also, studies limited to patients at risk of imminent death due to hypoxemia might suggest a role as salvage therapy, although these would be difficult to conduct.

The role of HFOV in critically ill neonates and adults has been informed by multiple, controlled, large-scale trials; unfortunately, such data are not available for the non-neonatal pediatric population. Consequently, there is a need for large-scale, multicenter, prospective, controlled study of HFOV in this population. Such study would likely confirm that HFOV is effective at raising \( \text{Pao}_2 \) while minimizing barotrauma in PARDS. However, future study must assess other essential clinical parameters such as mortality, ventilation duration, length of PICU and hospital stays, and long-term pulmonary function. In addition, given the heterogeneity of PARDS, it is important that such research attempt to identify which children are most likely to benefit from HFOV. Select subsets may benefit, even if an overall impact cannot be established. Such research should attempt to identify the optimal time for transition
to and from HFOV since this may be pivotal to any potential success. The support needed during HFOV, including sedation, NMB, vasoactive infusions, and potential complications such as pneumothoraces must also be assessed.

**INHALED VASODILATORS**

When given by the inhaled route, the effect of vasodilators is largely limited to adequately ventilated lung, with little systemic impact. Nitric oxide is a gaseous signaling molecule synthesized in the endothelium by nitric oxide synthase. It relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic-guanosine 3',5'-monophosphate (cGMP), which then leads to vasodilation. After inhalation, nitric oxide diffuses rapidly across the alveolar-capillary membrane into the subjacent smooth muscle of pulmonary vessels to activate soluble guanylate cyclase. This enzyme mediates many of the biological effects of nitric oxide and is responsible for the conversion of guanosine triphosphate to cGMP. The increased intracellular concentrations of cGMP relax smooth muscle via several mechanisms. The physiologic actions of cGMP are limited to its area of synthesis by its hydrolysis to GMP by cyclic nucleotide phosphodiesterases (PDEs) or by its export from the cell. Of the 11 reported PDE isozymes, PDE5 is considered to be the most active cGMP-hydrolyzing one in smooth muscle. Nitric oxide is avidly scavenged by hemoglobin on diffusing into the bloodstream, and is rapidly inactivated on its binding with hemoglobin. Consequently, the vasodilatory effect of iNO has minimal effect on the systemic vasculature. Disadvantages of iNO are possible lack of effectiveness, potential toxicity, availability, and expense.

Inhaled prostacyclin (epoprostenol) and alprostadil activate cyclic adenosine monophosphate-mediated reduction in intracellular calcium, causing vasodilation, but may also have antiinflammatory and antiplatelet effects. The oxygenation and hemodynamic effects are similar to those of iNO.

**Adult Data**

It has long been established that iNO raises $P_{A\text{O}_2}$ and lowers pulmonary artery pressures in ARDS patients. The data are more discouraging with respect to patient-centered outcomes such as ventilator-free days, length of stay, and survival. Two large trials and two meta-analyses have been published. In a European study limited to iNO responders (at least a 20% rise in $P_{A\text{O}_2}$) with ARDS ($P/F < 165$ mm Hg), those randomized to iNO had higher $P_{A\text{O}_2}$ levels and less severe hypoxemia, but were no more likely to experience reversal of ARDS or to survive. In a post hoc analysis, subjects managed conventionally were more likely to be alive and off the ventilator over time ($p < 0.01$). In another large trial, patients with ARDS ($P/F \leq 250$ mm Hg) and no significant nonpulmonary organ dysfunction were randomized to iNO (5 ppm) or placebo (nitrogen gas) for up to 28 days.\textsuperscript{15} Although $P_{A\text{O}_2}$ was higher with iNO initially, this effect was no longer observed at 48 hours. There was no substantial impact on ventilation duration or mortality. These results call into question the value of $P_{A\text{O}_2}$ response as a surrogate for more important outcomes such as survival.

In a meta-analysis of 1,142 patients enrolled in nine trials, iNO did not reduce mortality in ARDS regardless of severity.\textsuperscript{16} Varying the P/F threshold between 70

183
and 200 mm Hg failed to identify any cutoff at which iNO-treated subjects had lower mortality than control subjects. In another systematic review of 1,363 subjects (including both ARDS and pulmonary hypertension), iNO significantly increased the risk of acute kidney injury. The risk was greater with higher cumulative doses and in patients with ARDS. These data demonstrate that there is no role for iNO in most adult patients with ARDS, and even raise concern for harm. The effects on oxygenation and pulmonary artery pressures suggest that iNO could be useful in patients with life-threatening hypoxemia or right ventricular failure unresponsive to more conventional therapies such as paralysis, prone positioning, and low tidal volume ventilation.

There are fewer data on inhaled prostaglandins, and the quality of studies is poor. In a recent meta-analysis, inhaled prostaglandins were found to raise $P_{aO_2}$ and lower pulmonary artery pressure, but often cause hypotension. As with iNO, APRV, and HFOV, the clear oxygenation response has not been found to predict beneficial outcomes.

**Pediatric Data**

Until recently, an in-depth analysis of the pediatric literature demonstrated increased oxygen levels with iNO initiation, but no change in mortality or other clinically relevant outcomes (Table 4). Using a crossover design, Day compared the effects of iNO (10 ppm) in children ($n = 10$) requiring $PEEP > 6\ cm\ H_2O$ and $FiO_2 > 0.5$ with 12 control patients. Although there was an immediate response in pulmonary vascular resistance and OI, the oxygenation effects were not sustained in the patients initially randomized to iNO therapy. In contrast, the patients who initially served as controls had sustained increases in OI after 24 hours of receiving iNO. In another study, Dobyns and colleagues performed a prospective, multicenter, randomized controlled trial of 108 children with OI > 15 randomized to iNO 10 ppm or control. Half of the patients in the treatment group had no improvement in OI, and mortality was comparable between the two groups. As a result of these reports and other data, the PALICC panel recommended against the routine use of iNO in PARDS, but offered that it should be considered for children with pulmonary hypertension, severe right ventricular dysfunction, intractable hypoxemic respiratory failure, and as a bridge to ECLS. After those recommendations were released, Bronicki and colleagues published the results of a trial that randomized 55 pediatric patients with PARDS from nine centers to receive continuous iNO (5 ppm) or placebo. There was an increase in oxygen levels at 12 hours after initiation of iNO that did not persist at 24 hours. However, children who received iNO had decreased duration of mechanical ventilation, more days alive, and a greater rate of EMCO-free survival.

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Increased Oxygenation</th>
<th>Mortality</th>
<th>Outcomes</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1997 Single-center RCT with crossover N = 22</td>
<td>Yes</td>
<td>Unable to assess a difference</td>
<td>No ability to compare because controls were treated after 24 hours.</td>
<td>Immediate improvement in OI and decrease in PVR. No sustained improvement in initially treated group. Sustained improvement in initial control group after crossover to iNO. iNO dose 10 ppm.</td>
</tr>
<tr>
<td>Author</td>
<td>Study Type</td>
<td>N</td>
<td>Treatment</td>
<td>Comparison</td>
</tr>
<tr>
<td>--------</td>
<td>------------</td>
<td>---</td>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>Dobyns 1999</td>
<td>Multicenter RCT</td>
<td>108</td>
<td>Yes</td>
<td>No difference, although those with high OI considered treatment failures exited study.</td>
</tr>
<tr>
<td>Lopez-Herce Cid 2003</td>
<td>Single-center case series</td>
<td>55</td>
<td>Yes</td>
<td>P/F increased and OI decreased with iNO.</td>
</tr>
<tr>
<td>Ibrahim 2007</td>
<td>Single-center RCT</td>
<td>32</td>
<td>Yes</td>
<td>No difference.</td>
</tr>
<tr>
<td>Afshari 2011</td>
<td>Meta-analysis</td>
<td>1,303</td>
<td>Yes</td>
<td>No difference.</td>
</tr>
<tr>
<td>Bronicki 2015</td>
<td>Multicenter RCT</td>
<td>55</td>
<td>Yes</td>
<td>Days alive, ventilator-free days, and ECMO-free survival all improved in treated group.</td>
</tr>
<tr>
<td>Pappert 1995</td>
<td>Single-center case series</td>
<td>3</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Dahlem 2004</td>
<td>Single-center RCT with crossover</td>
<td>14</td>
<td>Yes</td>
<td>Children with acute lung injury treated with inhaled prostacyclin had improved oxygenation.</td>
</tr>
</tbody>
</table>

Abbreviations: iNO, inhaled nitric oxide; OI, oxygenation index; P/F, Pao2/Fio2 ratio; PVR, pulmonary vascular resistance; RCT, randomized, controlled trial.

The data regarding the use of inhaled prostaglandins in children are sparse. A single-case series of three children given both iNO and inhaled prostacyclin demonstrated a decrease in pulmonary artery pressure and an increase in Pao2. Additionally, a randomized, placebo-controlled, crossover, blinded study of 14 children who received escalating doses of epoprostenol (10–50 ng/kg/min) found a significant improvement in OI at the 30 ng/kg/min dose and a trend toward significance at the 20, 40 and 50 ng/kg/min doses with no adverse events.

**Recommendations**

In adults, there is no apparent role for iNO or inhaled prostacyclin for ARDS unless there is significant pulmonary hypertension. We recommend alternative rescue therapies (Figure 1), unless acute cor pulmonale is present. In such settings, inhaled prostacyclin is typically preferred because of its lower cost. In PARDS, the role of inhaled vasodilators is less well established. Although current recommendations
suggest that iNO should not be used routinely but only in special situations such as pulmonary hypertension or severe right ventricular dysfunction, recent data suggest a possibility of benefit. Since established risks are few, it may be considered as rescue therapy for severe refractory hypoxemia, particularly in the presence of pulmonary hypertension, or high suspicion for it.

**Additional Areas for Research**

For adults, the greatest interest in further study lies in treating patients with right ventricular dysfunction, with attention to patient-centered outcomes and risks of therapy interruption (which can precipitate acute hemodynamic collapse). For PARDS, appropriately powered studies are needed to best assess the role of iNO and aerosolized prostaglandins and their impact on clinically relevant outcomes, including mortality. Also, studying these therapies in the subset of patients with PARDS who have early echocardiographic evidence of pulmonary hypertension merits consideration.

**SURFACTANT**

Surfactant has two main functions in pulmonary physiology: It reduces the surface tension of the lung units and it aids in protecting against infection and inflammation. In acute hypoxemic respiratory failure, there is a relative paucity of surfactant activity. Consequently, it is biologically plausible that the exogenous administration of surfactant may improve outcomes in this disease state by raising \( \text{Pao}_2 \), reducing the level of PEEP required, or increasing lung compliance. Indeed, neonatal respiratory distress syndrome has been successfully treated with exogenous surfactant, which has revolutionized neonatal care. However, neonatal respiratory distress syndrome is purely a deficiency of surfactant, in contrast to non-neonatal lung injury, which is characterized by destruction and dysfunction of surfactant. Thus, the encouraging results of neonatal lung disease cannot be extrapolated to the non-neonatal patient population. Disadvantages of exogenous surfactant include delivery via endotracheal tube by an experienced clinician, the need for multiple doses, and its high cost. It has been associated with hypoxia, bronchospasm, air leaks, and hypotension.

**Adult Data**

Six randomized trials of surfactant have been reported in adults with ARDS, including several different products and administration methods; all have been negative. In the earliest study, synthetic surfactant (Exosurf) was aerosolized into the ventilator circuit. No physiologic effects were observed, and there was no change in longer-term outcomes. A second trial involved direct instillation of a semisynthetic product (Survanta), resulting in a modest rise in oxygenation, but no benefit with regard to important outcomes. Another synthetic surfactant (Venticute) was instilled in two trials, but without benefit. A subsequent attempt using a natural, porcine surfactant raised concern for harm related to instillation into the airway. A careful analysis of the limitations of all of these trials, subset analyses, and the pediatric experience led to a final adult trial in which a natural calf surfactant extract was instilled into the endotracheal tubes of subjects with early, direct lung injury (\( P/F \leq 300 \) mm Hg).\(^\text{18}\) Treatment failed to raise \( \text{Pao}_2 \) or improve length of stay or survival. Instillation often provoked transient hypoxemia or hypotension. The study was terminated after the
first interim analysis. Taken together, these studies demonstrate no role for surfactant as routine treatment for ARDS or as rescue for adult patients with critical hypoxemia.

**Pediatric Data**

Starting in the late 1990s, several small trials in children demonstrated trends toward increased oxygenation, shorter duration of mechanical ventilation, and shorter PICU stays, but no mortality differences with the use of surfactant (Table 5). These studies led to a 22-center randomized controlled trial of surfactant in pediatric hypoxemic respiratory failure. In a trial of 153 children, surfactant use was associated with higher Pao$_2$ and a decrease in mortality. However, there was no difference in ventilator-free days (the primary outcome measure of the trial), and there was a disproportionate number of immunocompromised patients in the control arm, rendering the difference in mortality statistically insignificant in multivariable analysis (Table 5). As a result, a large randomized controlled trial with both a pediatric and adult arm was conducted. Both arms, which used a concentrated form of calf surfactant, were terminated early secondary to an interim analysis demonstrating futility. In the pediatric arm, surfactant therapy failed not only to demonstrate an effect on mortality, but also failed to increase oxygenation. The lack of oxygenation effect is particularly noteworthy because most other pediatric surfactant trials had demonstrated higher Pao$_2$ levels. Most recently, a blinded, randomized controlled trial limited to children younger than two years demonstrated higher Pao$_2$, but no other outcome changes (Table 5). Finally, a recently published Cochrane analysis of surfactant use in bronchiolitis suggested beneficial effects on gas exchange, mechanical ventilation duration, and PICU length of stay. However, the authors acknowledge that no definitive conclusions can be drawn because the number of published trials is limited and their analysis consisted of only 79 patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Description</th>
<th>Increased Saturation</th>
<th>Mortality</th>
<th>Outcomes</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson 1996</td>
<td>Multicenter open-label observational N = 29</td>
<td>Yes</td>
<td>14%</td>
<td>Immediate improvement in oxygenation allowed weaning of ventilator support.</td>
<td>Three patients developed air leaks. Bovine surfactant 80 mL/m$^2$.</td>
</tr>
<tr>
<td>Luchetti 1998</td>
<td>Single-center RCT N = 20</td>
<td>Yes</td>
<td>No deaths</td>
<td>Decreased inspiratory pressures, Porcine surfactant 50 mg/kg.</td>
<td></td>
</tr>
<tr>
<td>Wilson 1999</td>
<td>Multicenter unmasked RCT N = 42</td>
<td>Yes</td>
<td>No difference</td>
<td>Decreased ventilation time, shorter PICU stay.</td>
<td>Bovine surfactant 80 mL/m$^2$.</td>
</tr>
<tr>
<td>Tibby 2000</td>
<td>Single-center RCT N = 19</td>
<td>Yes</td>
<td>No deaths</td>
<td>Improvements in ventilation indices.</td>
<td>All neonates with RSV infection. Median age 4 weeks. Bovine surfactant 100 mg/kg.</td>
</tr>
<tr>
<td>Luchetti 2002</td>
<td>Multicenter RCT N = 40</td>
<td>Yes</td>
<td>No deaths</td>
<td>Treated patients had increased compliance, shorter mechanical ventilation course, and shorter PICU stay.</td>
<td>Earlier treatment led to more robust response. All patients had RSV infection. Porcine surfactant 50 mg/kg.</td>
</tr>
<tr>
<td>Lopez-herce Cid 2003</td>
<td>Single-center case series N = 17</td>
<td>Yes</td>
<td>No difference</td>
<td>P/F increased and OI decreased with surfactant.</td>
<td>Three-pronged study with prone position, surfactant, and iNO.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>N</td>
<td>Results</td>
<td>Conclusion</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>--------------</td>
<td>-------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Moller</td>
<td>2003</td>
<td>Single-center followed by multicenter RCT</td>
<td>N = 19</td>
<td>Yes, no difference in survival mortality and need for rescue therapies, but neither obtained statistical significance.</td>
<td>Increased oxygenation sustained only in patients with P/F &lt; 100 and &gt; 65 mm Hg and those without pneumonia. Bovine surfactant 100 mg/kg.</td>
</tr>
<tr>
<td>Wilson</td>
<td>2005</td>
<td>Multicenter RCT</td>
<td>N = 153</td>
<td>Yes, decreased with surfactant therapy</td>
<td>Immune compromised patients unequally distributed between treatment groups. Controlling for immunocompromised state rendered mortality difference statistically insignificant. Bovine surfactant 80 mL/m².</td>
</tr>
<tr>
<td>Thomas</td>
<td>2012</td>
<td>Multicenter RCT</td>
<td>N = 165</td>
<td>Yes, no deaths in either group</td>
<td>Study limited to children &lt; age two years. Lucinactant (synthetic) surfactant 175 mg/kg.</td>
</tr>
<tr>
<td>Wilson</td>
<td>2013</td>
<td>Multicenter RCT</td>
<td>N = 109</td>
<td>No, no difference</td>
<td>Closed prematurely due to futility. Concerns that more concentrated form of surfactant may have led to lack of effect on oxygenation. Bovine surfactant 30 mg/cm.</td>
</tr>
<tr>
<td>Jat</td>
<td>2015</td>
<td>Meta-analysis of surfactant in bronchiolitis 3 studies</td>
<td>N = 79</td>
<td>Yes, no difference in ventilation duration or length of PICU stay.</td>
<td>Decrease in length of PICU stay. Excluding study with heterogeneity resulted in decreased mechanical ventilation duration. Suggest studies looking at cost-effectiveness of treatment.</td>
</tr>
</tbody>
</table>

Abbreviations: iNO, inhaled nitric oxide; OI, oxygenation index; P/F, Pao₂/Fio₂ ratio; PICU, pediatric intensive care unit; RCT, randomized, controlled trial; RSV, respiratory syncytiatal virus.

**Recommendations**

For adult ARDS, we do not recommend surfactant in any clinical setting. In PARDS, research suggests that, when properly delivered and in sufficient dose, exogenous surfactants may raise Pao₂, but have no effect to decrease mechanical ventilation duration, PICU length of stay, or mortality. Consequently, surfactant cannot be recommended for routine therapy in PARDS.

**Additional Areas for Research**

The somewhat encouraging early results in pediatric patients suggest that additional, adequately powered clinical trials using appropriate formulations and delivery methods may be considered. However, further research should focus on specific pediatric patient populations that may be likely to benefit from exogenous surfactant, paying careful attention to dosing, strength, and delivery methods.

**EXTRACORPOREAL LIFE SUPPORT**

ECLS for patients with ARDS consists of ECMO, in which the focus is on maintaining an acceptable Pao₂, or extracorporeal CO₂ removal (ECCO₂R), in which the extracorporeal circuit is used to enhance lung-protective ventilation. The most common circuit design is venovenous ECLS, in which blood is withdrawn, generally through a central vein, pumped through a membrane lung, and returned, usually to
the right atrium. Venoarterial ECLS is used when the circulation is impaired, a very unusual circumstance in adult ARDS. Finally, blood can be withdrawn from an artery and returned to a vein (arteriovenous ECLS), an approach used most often for ECCO$_2$R when the goal is ultraprotective ventilation. These interventions are highly invasive, with significant risks of complications. The most common complication is bleeding due to the anticoagulation used to prevent clotting within the circuit. Less commonly, ECLS is complicated by thrombosis, infection, intracranial hemorrhage, ischemic stroke, or catastrophic circuit failure.

ECLS is most often considered a rescue therapy, used when adequate gas exchange cannot be achieved or when ventilator settings are required that violate precepts of lung protection. ECLS may allow for lung recovery by keeping the patient alive while minimizing additional ventilator-induced lung injury. ECCO$_2$R has also been proposed as a means to reduce tidal volume to 4 mL/kg PBW or lower for patients with severely reduced lung compliance. Finally, ECLS can serve as a bridge to transplant.

**Adult Data**

Experience with ECLS for ARDS increased greatly with the 2009 H1N1 influenza pandemic. At regional referral centers in Australia and New Zealand, one-third of ventilated patients were also treated with ECMO; 79% of them survived. Using a cohort study of British patients, mortality in those referred for ECMO was compared with that of matched patients who were not referred. Among patients referred for ECMO (86% of whom actually received it), mortality was only 24%, compared with 53% in those not referred ($p = 0.006$). A similar analysis of the French experience revealed no difference in mortality, although ECMO patients who could not be matched (younger and more severely ill) were, paradoxically, more likely to survive.

There has been a single prospective, randomized trial of ECMO for adult ARDS using modern approaches, the CESAR trial.$^{19}$ Subjects were aged 18 to 65 years, with severe, potentially reversible ARDS defined by a Murray Lung Injury Score (based on P/F, PEEP level, respiratory system compliance, and chest imaging) of ≥ 3, or by uncompensated hypercapnia (pH < 7.2 despite optimal management). Patients were excluded if injurious ventilator settings had been used for more than seven days.

Subjects allocated to the treatment arm (n = 90) were transported to a single ECMO center, managed optimally for up to 12 hours, and, if unimproved, treated with venovenous ECMO (68 received the treatment). Those randomized to usual management (n = 90) were treated in a conventional medical center where best practices were advocated but not mandated. One limitation of this approach is that practices differed between the conventional centers and the ECMO center in the use of lung-protective ventilation and in other treatments. Nevertheless, those referred for ECMO were more likely to survive to six months without disability (the prespecified primary outcome).$^{19}$ Two deaths were reported in ECMO subjects: one subject died during transport due to equipment failure, and one died in part because of a major vessel perforation during cannulation.

**Pediatric Data**
Research in ECMO use for non-neonatal acute lung injury dates back to the 1980s, when Bartlett conducted the landmark “play the winner” trial. In that trial, the first patient was randomized to conventional ventilation and died; the subsequent 11 patients received ECMO and survived, at which point the trial was discontinued. However, since then, controlled research to assess the effect of ECMO in non-neonatal children with PARDs has been limited by a number of factors, including difficulty achieving enrollment, a lack of equipoise, and changes in lung-protective strategies over the past few decades.

The Extracorporeal Life Support Organization (ELSO) maintains a registry that collects ECMO data from 226 institutions. Much of the current ECMO knowledge has come from the ELSO registry. ELSO data suggest that survival rates for pediatric patients requiring ECMO for respiratory causes range between 51% and 69%, depending on the diagnosis. This survival rate does not seem to be improving over time despite improvements in ECMO technology. Data from the neonatal population suggests decreased long-term morbidity with ECMO when compared to those treated with more conventional strategies.

In 2011, Zabrocki and colleagues published a review from the ELSO registry of 3,213 children aged one month to 18 years who underwent ECMO for acute respiratory failure. Overall survival rate was 57%. There was no change in mortality during the study (1993–2007), but there was an increase in the number of children with comorbidities undergoing ECMO, suggesting a trend toward using ECMO in more complex patients. The use of mechanical ventilation for more than 14 days before ECMO was associated with lower survival rate (33%). Survivors also had a higher pH (7.31 vs. 7.27) when ECMO was started. With regard to ECMO type, 64% of children underwent venoarterial ECMO. However, there was a trend toward increasing use of venovenous ECMO, which was associated with improved survival. One year later, Dalton published an update that included ELSO registry data. Among the 5,220 pediatric respiratory cases reported, 65% were able to be successfully decannulated and 56% survived to discharge or transfer.

More data are needed to inform the optimal use of ECMO. Evidence-based data ranging from criteria that identify patients most likely to benefit from ECMO to the technologic and therapeutic intricacies of ECMO must be developed. Post hoc analysis and case control studies have found the OI to be an independent predictor of mortality. Historically, an OI > 40 has suggested ECMO consideration; however, emerging data linking OI to mortality has caused experts to speculate that ECMO should be considered at a lower OI threshold. Additionally, little data exist to inform management strategies such as the optimal approach to anticoagulation, in terms of both therapy and monitoring, as well as appropriate medication dosing. Moreover, the scant literature that is available is primarily single-center, retrospective data.

Recommendations

For adults, the most careful interpretation of the CESAR results is that, for patients with severe ARDS, outcome is improved by referral to an ECMO-capable center specializing in the treatment of lung failure. How much of the improvement can be attributed to ECMO itself remains uncertain. At the same time, the treatment is costly and risks serious adverse events. Nevertheless, these are positive findings that support the use of ECMO before other unproved rescue treatments such as HFOV,
APRV, or inhaled vasodilators. Therefore, for adult patients failing treatment with prone ventilation and NMB, we advocate transfer to an ECMO center. Furthermore, even for patients in whom prone ventilation and NMB are indicated, a case may be made that ECMO should be considered instead. As ECMO technology and experience continue to improve, outcomes may as well.

In PARDS, there are no evidence-based criteria to support the transition to ECMO and very little data to inform its use. The PALICC panel offered several points of guidance. At a minimum, ECMO should be considered in children with respiratory failure when the underlying cause is reversible, and the ventilator support required for adequate gas exchange is considered toxic to the lungs (Table 6). Accurately establishing the reversibility of lung disease can be problematic. Other considerations for ECMO candidacy include comorbidities, overall prognosis, the availability of ECMO in PICUs, and the risk of transporting critically ill children to an ECMO center. Finally, ECMO may also be considered as a bridge to transplant.

### TABLE 6. Criteria for Considering Rescue Therapies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fio&lt;sub&gt;2&lt;/sub&gt; &gt; 0.6</td>
<td></td>
</tr>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt; &lt; 60 mm Hg</td>
<td></td>
</tr>
<tr>
<td>OI ≥ 16</td>
<td></td>
</tr>
<tr>
<td>SaO&lt;sub&gt;2&lt;/sub&gt; &lt; 88%</td>
<td></td>
</tr>
<tr>
<td>OSI ≥ 12.3</td>
<td></td>
</tr>
<tr>
<td>P/F &lt; 150 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Uncompensated hypercapnia</td>
<td></td>
</tr>
<tr>
<td>Pplat &gt; 28 cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td></td>
</tr>
<tr>
<td>Right ventricular dysfunction attributed to ARDS</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ARDS, acute respiratory distress syndrome; Fio<sub>2</sub>, fraction of inspired oxygen; OI, oxygenation index: (Fio<sub>2</sub>)(MAP)(100)/PaO<sub>2</sub>; OSI, oxygen saturation index: (Fio<sub>2</sub>)(MAP)(100)/SaO<sub>2</sub>; Pao<sub>2</sub>, partial pressure of arterial oxygen; P/F, PaO<sub>2</sub>/Fio<sub>2</sub> ratio; Pplat, ventilator airway plateau pressure; SaO<sub>2</sub>, percent oxygen saturation of arterial hemoglobin; S/F, SaO<sub>2</sub>/Fio<sub>2</sub> ratio.

### Additional Areas for Research

The limitations of the CESAR trial have left many intensivists unconvinced of its findings. At the same time, newer techniques, such as dual-lumen cannulas, awake and ambulatory ECMO, and refined anticoagulation protocols have provoked new enthusiasm. In both adults and children, there is a particular role for defining anticoagulation goals, best ventilator settings to achieve lung rest, and the role of extubation and ambulation. ECMO should be compared to the current state-of-the-art lung-protective ventilation, and both ECMO and control arms should be treated in the same centers with the same treatment teams to control for these factors. Evidence-based guidelines are needed regarding the parameters used to determine the appropriateness of ECMO. Ancillary therapies while on ECMO, such as bronchoscopy, sedation, medication dosing, and nutritional considerations, are also very relevant. Finally, research into understanding the best time to transition a patient off ECMO support is needed to provide optimal care.

### SUMMARY OF RESCUE STRATEGIES FOR ARDS PATIENTS FAILING CONVENTIONAL VENTILATION

The general application of rescue therapies to all ARDS cases is likely to result in
some combination of failed clinical use, the acceptance of undue risks, and the
incurrence of unnecessary costs. In attempting to identify situations in which
nonconventional and adjunctive therapies may be of most benefit as rescue
strategies, it is important to recognize that therapies that are beneficial in one
population may not be beneficial in another. Furthermore, populations are not
necessarily distinct and dichotomous; the use of these therapies should be based on
underlying physiology, recognizing that age and developmental status influence that
physiology.

It is important to identify the clinical criteria that suggest a need to implement
nonconventional or adjunct rescue therapies (Table 6). Although not firmly
established with rigorous scientific data, there are commonly used and generally
accepted criteria (Table 6). We emphasize, however, that current targets for
acceptable oxygenation are not evidence-based. Some have even proposed that
permissive hypoxemia could be preferable to rescue therapies, although data are
inadequate from which to draw conclusions. It can be debated whether allowing the
Sao\textsubscript{2} to hover around 85%, for example, might not produce better results than many
of the available rescue therapies. Nevertheless, at some admittedly arbitrary
threshold of inadequate oxygenation or ventilation, adjunctive therapies should be
considered (Table 1). It is important to recognize that the ability to improve oxygen
saturation and Pao\textsubscript{2} has not equaled improved survival or other clinically relevant
outcomes, so we urge clinicians not to rely solely on oxygenation response as a way
to judge whether therapies are beneficial.

Given the limited data to inform the use of rescue therapies, there is no consensus
regarding how to prioritize or sequence them. Moreover, local expertise can greatly
affect which treatments are preferred and, perhaps, successful. One approach for
adults with ARDS is presented in Figure 1. NMB and prone ventilation are
recommended as the initial rescue intervention based on data demonstrating
improved survival. ECLS follows next, but this elevates the controversial results of
the CESAR trial over cost and invasiveness. For pediatric patients, proposing such
an algorithm is speculative and clearly unsubstantiated given limited high-quality
data. At best, an algorithm for children can be offered that would attempt only to
prioritize physiologic reasoning (inhaled vasodilators for right ventricular dysfunction),
ease of use (APRV), or safety. We have elected not to do so.

In sum, the data to inform the appropriate use of rescue therapies in refractory ARDS
are limited. Well-conducted trials in children have consistently resulted in negative
findings. This inability to demonstrate an effect may be, at least in part, the result of
the relatively small and heterogeneous study populations that are characteristic of
PICUs. Innovative and alternative study designs may be necessary to inform
practice; comparison effectiveness trials may represent one such alternative. Data
informing the use of rescue therapies for adults with ARDS is more abundant,
perhaps because of the larger patient population or the relatively higher baseline
mortality. Because many, if not all, of these interventions require experience and
expertise of an entire multidisciplinary team to be most effective, appropriate study
may require that each site use the intervention with which they are most comfortable
and experienced. Moreover, given that case reports and anecdotal experience
suggest that each of these interventions has the ability to be effective, a better goal
may be to identify which subset of patients respond to which therapies rather than
trying to identify one therapy for the overall ARDS population. No intensivist would
refrain from attempting rescue therapies in patients with acute pulmonary failure who fail conventional therapy, particularly in the setting of single-organ disease. Consequently, data informing the best clinical use of these therapies are needed.

KEY POINTS

- A host of rescue therapies are available for adults and children with ARDS who fail conventional treatment.
- A clear understanding of the physiology/pathophysiology impacted by these therapies will help the clinician use them most effectively.
- These therapies must be implemented with a healthy balance of the imposed risk and the likelihood of benefit.
- These therapies are implemented to acutely increase oxygenation and/or enhance \( \text{CO}_2 \) elimination, but such acute, short-term responses do not necessarily equate with improved, clinically relevant, patient-centered outcomes.
- The use of continuous neuromuscular blockade (NMB) for 48 hours has been found to improve survival in adults with ARDS. The two mechanisms that most likely explain this benefit of NMB are improved patient-ventilator synchrony and the prevention of pendelluft.
- The PROSEVA trial demonstrated that, combined with lung-protective ventilation, early and prolonged prone positioning improved survival of ARDS patients with \( \text{P/F} < 150 \text{ mm Hg} \).
- High-frequency oscillatory ventilation (HFOV) and airway pressure release ventilation (APRV) are two nonconventional forms of ventilation that attempt to maintain high mean airway pressure while minimizing the extremes of inspiratory pressures. APRV facilitates spontaneous patient respirations, affording it a potential advantage over HFOV.
- The role of inhaled pulmonary vasodilators is still being established. In adults, their only role seems limited to those with severe pulmonary hypertension, life-threatening hypoxemia, or right ventricular failure unresponsive to more conventional therapies such as paralysis, prone positioning, and low tidal volume ventilation. Their role in children is less well established. Current recommendations for inhaled nitric oxide are that it should be considered only for children with pulmonary hypertension, severe right ventricular dysfunction, intractable hypoxic respiratory failure, or as a bridge to extracorporeal life support.
- Exogenous surfactant therapy has been found to have no substantial benefit. Its use cannot be supported at this time.
- Extracorporeal life support is also being implemented as rescue therapy in patients with refractory ARDS. In adults, transfer to an ECMO-capable center is associated with improved outcomes. Little data are available for children; registry data suggest that mortality remains high among non-neonatal children treated with ECMO for respiratory failure.
- Determining the most appropriate role of rescue therapies for severe ARDS remains a challenge. Significant issues include the relatively small and heterogeneous patient population, the difficulties of enrolling such clinically tenuous patients in trials, and the lack of equipoise. These issues may be exacerbated for the pediatric population and confounded by a lower overall ARDS-related mortality among children.
• The ability to detect, or not detect, a benefit of rescue therapies among a broad, heterogeneous population does not necessarily inform its value in an individual patient who fails conventional therapy.

• Rescue therapies are devised to prevent death due to catastrophic gas exchange failure or to allow reductions in other noxious treatments in the hope of improving outcomes. Improvements in oxygenation and/or CO₂ elimination effected by rescue therapies should be used in a timely manner to minimize potentially toxic support.

REFERENCES


OBJECTIVES

- Describe the main goals and objectives of noninvasive ventilation (NIV) and continuous positive airway pressure (CPAP)
- Discuss patient selection as a major factor in the successful delivery of NIV
- Distinguish the different types of ventilators and mask interfaces commonly used in the delivery of NIV
- Discuss the importance of proper communication with the patient to achieve compliance with therapy
- Describe the initiation and subsequent management of NIV and CPAP
- Discuss the proper way to apply the mask interface to the patient
- Discuss the process of NIV/CPAP discontinuation
- Discuss where NIV should be administered
- Contrast NIV with high-flow nasal cannula

INTRODUCTION

Noninvasive ventilation (NIV) is an application of positive pressure, in the absence of an endotracheal tube or tracheostomy tube, to augment alveolar ventilation, improve oxygenation, assist cardiac function, increase lung volume, and unload respiratory muscles. It is applied using a mask, helmet, or other noninvasive interface to the patient’s upper airway. During NIV, positive pressure increases during the breath’s inspiratory phase and returns to an elevated baseline during exhalation. This application of positive pressure during inspiration unloads the work imposed on the respiratory muscles. When only the expiratory pressure is elevated above atmospheric pressure, it is referred to as continuous positive airway pressure (CPAP). Increasing CPAP increases the lungs’ resting volume or functional residual capacity, mean airway pressure, and intrathoracic pressures. It can also be used to splint open the upper airway in patients with obstructive sleep apnea. Unlike NIV, CPAP does little to decrease the patient’s work of breathing (WOB) unless it counterbalances auto-positive end-expiratory pressure (auto-PEEP), reduces excessive drive to breathe, or helps clear pulmonary edema. CPAP alone is most commonly used to augment resting lung volume and recruit lung units, thereby supporting oxygenation.

There is strong evidence to support the use of NIV, especially in the setting of acute cardiogenic pulmonary edema (ACPE) and chronic obstructive pulmonary disease (COPD) exacerbations. Despite evidence supporting its use in various disease states, many questions remain. Clinicians often struggle with selecting initial settings and with intolerance of the interface during subsequent management. This chapter will provide a logical rationale for clinical adjustments to achieve desired clinical
outcome objectives.

**CLINICAL VIGNETTE**

**Case**

A clinician who is part of the rapid response team is called to the bedside of a 59-year-old Caucasian man who was recently admitted to the general care ward from the emergency department for shortness of breath due to congestive heart failure. The nurse informs the clinician that the patient has progressively worsened over the past few hours. He is sitting on the edge of his bed, awake, alert, and oriented to time and situation. He is diaphoretic, very anxious, and is speaking in short sentences. He appears well-nourished.

Vital signs are: heart rate 117 beats/min, respiratory rate 28 breaths/min, blood pressure 160/110 mm Hg, temperature 37.4°C (99.4°F), oxygen saturation (SpO₂) 83% on nonrebreathing mask at 15 L/min. Jugular vein distension is noted. Cyanosis is noted in lips and gums. Chest inspection reveals equal bilateral chest expansion with no tracheal shift. Auscultation reveals fine crackles in the bases with wheezing on expiration. There is ++ pitting edema in the ankles, and peripheral cyanosis in nailbeds of hands and feet.

Arterial blood gas results are: fraction of inspired oxygen (FiO₂) unknown, with oxygen delivered by nonrebreathing mask at 15 L/min, pH 7.53, partial arterial carbon dioxide pressure 27 mm Hg, bicarbonate 23 mEq/L, partial arterial oxygen pressure 46 mm Hg, arterial oxygen saturation 84%. Because of the clinical findings, the decision is made to initiate NIV. The charge nurse on the floor states that patients receiving NIV must be transferred to the intensive care unit (ICU). The ICU team is alerted, and the patient will be transferred upon bed availability.

**Discussion**

There is strong evidence supporting the use of NIV in ACPE.² Based on the likelihood that this patient has ACPE, the decision is made to implement NIV. Although it is still unknown if the early application of NIV is more advantageous than later application,³ it is reasonable to begin it now based on the clinical findings. Clinicians are faced with multiple decisions after initial patient selection has been made.⁴ Initially, the type of ventilator must be chosen. In most modern ICU settings, clinicians may use either critical care ventilators (typically associated with invasive mechanical ventilation) or noninvasive ventilators (specifically designed for noninvasive ventilatory support).

After a ventilator is chosen, the next step is to choose the proper interface. This is important because it enables the clinician to provide effective therapy that the patient can tolerate. Although nasal masks are often used in outpatient treatment of sleep apnea, interfaces that span the nose and mouth are more suitable for the active ventilatory support needed in the hospital. Once equipment decisions have been made, the patient must be informed of the therapy. Providing instruction and reassurance to the patient may increase the likelihood of the patient’s cooperation. Once the patient understands the therapy, ventilator settings must be chosen. This process is empirically determined and dynamic, since settings almost always need to be adjusted for patient comfort and tolerance. Once initial settings are selected, the
clinician must apply an interface. Depending on the patient’s ability to cooperate, this can be done in several ways, including allowing the patient to hold the interface until he/she can acclimate to the therapy. It is also important to eliminate leaks while not overtightening the interface. Once the interface is secured, the settings usually must be adjusted to meet therapeutic objectives. Frequent reassessment and adjustment may be necessary, but these should lessen significantly after the first few hours. Beyond ventilator settings and choice of interface, measures are taken to prevent humidity deficits and skin breakdown.

**Major Goals and Objectives of Noninvasive Ventilation**

In the acute setting, the major goals of NIV are to decrease WOB, improve gas exchange, and avoid endotracheal intubation. By avoiding intubation, NIV may decrease the incidence of hospital-acquired infections and help reduce mortality.

It is important to understand when to avoid NIV. Patients who are apneic or who are unable to protect their airway from aspiration are not candidates for NIV. (Comatose patients are rarely treated with NIV unless airway intubation has been declined.) In addition, hemodynamically unstable patients and those with facial abnormalities impacting device interface (trauma, anatomy, burns) should be excluded. Patients receiving NIV should also be cooperative and able to manage their own secretions (Table 1).

**TABLE 1. Contraindications to NIV**

- Apnea (respiratory arrest)
- Inability to protect airway
- Hemodynamic instability
- Facial abnormalities causing improper mask fit
- Noncooperation
- Excessive secretions
- Impaired mental status
- Recent upper airway/gastrointestinal surgery

**Patient Selection**

A major factor in successful noninvasive mechanical ventilation is patient selection. Data is continually evolving that either supports or refutes the use of NIV for various diseases and conditions.

**EXACERBATIONS OF COPD AND ACPE**

There is a vast body of evidence supporting the use of NIV in exacerbations of COPD and ACPE. The number needed to treat (NNT) to impact survival for patients with COPD exacerbation is 11; for ACPE, it is 30. The use of NIV in these two conditions is no longer debated if there are no contraindications. More research is needed to best understand when therapy should be initiated.

**ACUTE ASTHMA**

The role of NIV in acute asthma is not well defined. The use of NIV during life-threatening asthma has been shown to decrease the use of mechanical ventilation.
Other studies have shown success in using NIV for asthmatic patients with hypercapnia and intolerably increased WOB. In these studies, a low number of patients (19 of 112) were intubated. NIV may be considered as an alternative to intubation in patients who have failed standard therapy, to avoid intubation in patients with mild to moderate respiratory failure who do not immediately need ventilatory support, to prevent respiratory failure when gas exchange is not severely impaired, and to improve bronchodilation. The impact of NIV on asthma mortality is unknown. More investigation is needed.

**IMMUNOCOMPROMISED PATIENTS WITH ACUTE HYPOXEMIC RESPIRATORY FAILURE**

Evidence supports the use of NIV in immunocompromised patients who require respiratory support. NIV in this patient population may help prevent endotracheal intubation. The mortality benefit of NIV is controversial. Further investigation is warranted.

**POST-EXTUBATION**

NIV has been shown to prevent extubation failure in high-risk patients, prevent reintubation after extubation when failure occurs, and facilitate earlier extubation. Patients deemed to be at high risk (hypercapnia, congestive heart failure, multiple comorbid conditions) of extubation failure may benefit the most from NIV (Table 2). In fact, in these patients, a significant reduction in mortality has been reported, with an NNT of 10.4

<table>
<thead>
<tr>
<th>TABLE 2. Post-Extubation NIV: Patients at High Risk of Extubation Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>♦ Age 65 years and older</td>
</tr>
<tr>
<td>♦ Clinical conditions: congestive heart failure, ineffective cough, excessive secretions, upper airway obstruction, comorbid conditions, hypercapnia, cardiac failure (causing initial intubation)</td>
</tr>
<tr>
<td>♦ Previously failed spontaneous breathing trials</td>
</tr>
</tbody>
</table>

**PRE-INTUBATION**

Since patients are typically preoxygenated before endotracheal intubation, it is reasonable to use NIV for this purpose. Patients preoxygenated with NIV before intubation have been shown to experience fewer oxyhemoglobin desaturations during intubation and immediately after intubation.19

**POSTOPERATIVE ACUTE RESPIRATORY FAILURE**

NIV may be used to treat and prevent acute respiratory failure postoperatively. Data suggest that NIV is effective in the treatment of postoperative acute respiratory failure, with an NNT of 11. Mortality was not reduced when used preventively.4

**ACUTE RESPIRATORY DISTRESS SYNDROME**

NIV failure is high in patients with severe acute respiratory distress syndrome (ARDS), especially with coexisting sepsis. NIV in ARDS should be confined to patients with mild disease and, even then, attempted only with close observation and careful monitoring.
**PALLIATIVE CARE**

The use of NIV during palliative care is challenging. Clinicians must consider its actual benefits and objectives and must consider the patient’s well-being, family experience, patient/family satisfaction, and the caregiver’s perspective. Regardless of the purpose of NIV—whether as life support, avoidance of intubation, or as a palliative measure—the goals of care should be explicitly clear. Parameters for success and failure should be set by experienced personnel in the appropriate time frame and setting. 

**OTHER USES OF NIV**

- Bronchoscopy
- Community-acquired pneumonia
- Obesity hypoventilation syndrome
- Trauma
- Long-term applications
  - Nocturnal hypoventilation
  - Restrictive thoracic diseases
  - Neuromuscular disease (amyotrophic lateral sclerosis)

**Ventilator Types**

When a patient has been identified for NIV, clinicians must decide what equipment is necessary to deliver it. They may use either critical care ventilators or noninvasive ventilators. Some major considerations when making this decision are the degree of leak compensation that each device can provide, familiarity with the device, monitoring capabilities, and cost.

Noninvasive ventilators use a single-limb circuit designed to deliver a constant but variable flow of gas to the patient. The circuit contains a leak port that allows for passive exhalation and carbon dioxide (CO$_2$) removal from the circuit. The leak port is generally located in the circuit near the patient or inside the interface itself. Noninvasive ventilators are specifically designed to overcome some degree of air leak, which enables them to trigger and cycle appropriately.

Because of the way CO$_2$ is flushed from the single-limb circuit, caution must be taken when using low baseline pressures, which may allow for significant rebreathing of CO$_2$ from the circuit. In fact, most devices will not allow the baseline pressure to be set below 4 cm H$_2$O, the minimum level needed to clear the mask and circuit of CO$_2$. Increased baseline pressures may further reduce the likelihood of CO$_2$ rebreathing.

Noninvasive ventilators used in acute care typically come equipped with internal blenders that allow for the precise delivery of FIO$_2$. Nomenclature for noninvasive ventilators may be different from that of critical care ventilators; it is important to understand the similarities and differences (Table 3). Because of the variability in modes and settings, clinicians should familiarize themselves with the nuances of each device and its associated modes.

<table>
<thead>
<tr>
<th>Behavior</th>
</tr>
</thead>
</table>
Critical care ventilators are commonly available in critical care units. In contrast to noninvasive ventilators, critical care ventilators use dual-limb circuits with a separate exhalation valve, which limits the potential for rebreathing CO₂. Staff should be very familiar with their operation. Most are equipped with internal blenders that allow for precise FiO₂ delivery.²

Although generally outperformed by noninvasive ventilators with regard to synchronization, leak compensation on some advanced and modern critical care ventilators improve synchronization and effectively overcome associated leaks.² Again, this is a major concern when choosing a ventilator to deliver NIV. If leaks are too great for the machine to overcome, issues with triggering and cycling may lead to failure.

It must be emphasized that clinicians using NIV clinically should understand the device in terms of nomenclature, mode behaviors, and leak compensation capabilities.

**Interface**

Many types of NIV masks are commercially available (Figure 1). The interface provides the mechanism for pressurized gas to be delivered from the ventilator circuit to the patient’s upper airway. Noninvasive interfaces are designed as clear, hard plastic devices with large cushions with soft inner lips around them that form a seal around the patient’s face when secured with the headgear. The cushion and soft inner lips allow for comfort and reduce the likelihood of skin breakdown.

*Figure 1.* Devices for delivery of NIV
Clinicians must select the proper interface by considering facial shape, staff experience, patient preference (if possible), and equipment compatibility and availability. In the setting of acute respiratory failure, oronasal and total face masks are generally recommended. Switching to a different interface based on individual patient tolerance is frequently necessary. In hirsute patients and those with facial irregularities or deformity, finding a properly fitting mask can be challenging. Standard masks may be sized inappropriately for the patient. This results in leaks around the eyes or lips, which may impact patient compliance. Sizing guides are available with each mask (Figure 2). Clinicians should be familiar with their institution’s equipment as well as with their ventilators. Proper use of the sizing guides and gauges could potentially reduce cost, avoid wasting equipment, and maximize patient comfort.

**Figure 2.** Assessing mask size
The interface must be compatible with the ventilator circuit in order to prevent CO₂ rebreathing. Mask interfaces that use an open, single-limb circuit are specifically designed for this application, by virtue of the exhalation port. Closed, dual-limb circuits do not need a leak port because of the exhalation valve. Mask interfaces may be packaged and colored differently according to purpose. Clinicians must avoid combining the wrong interface and circuit; this could potentially be hazardous. The caregiver therefore should identify the exhalation port and check circuit compatibility before clinical application of the assembly.

It is important to realize that current NIV mask designs allow clinicians to avoid overtightening the straps. Facial skin breakdown can occur from overtightening. This further underscores the need for proper mask sizing. When skin breakdown is a real concern, consider adjusting the forehead arm (if applicable), application of skin barrier, or changing the interface entirely (eg, switching from oronasal mask to total face mask). Loosening the straps may also be an option since the NIV ventilators/modes should compensate for small leaks.

Finally, caregivers must be cognizant of the interference that the mask interface may have on communication, expectoration of secretions, and eating/drinking. NIV masks often come with headgear that allows the mask to be removed relatively easily. In the event of removal for any reason, it is important that the mask be replaced in the correct position.

Informing the Patient/Patient Compliance

Patient compliance is paramount to the success of NIV. Providing instruction and reassurance during NIV initiation may increase the likelihood that the patient will cooperate. Clinicians should clearly explain the procedure and the sensations that the patient may feel on NIV initiation.

Choose your settings

Little data are available to guide the selection of proper NIV settings. Before determining settings, the clinician must decide what is being treated: hypercapnia, refractory hypoxemia, or both. If refractory hypoxemia is the main concern, such as
with ACPE, CPAP may be used. Mask CPAP can decrease preload, decrease afterload, improve lung compliance, counterbalance auto-PEEP, and decrease intrapulmonary shunt. It is important to note that, while CPAP use is common in ACPE, NIV can be used as well, since both have shown improvements in survival and intubation rate.

When hypercapnia is present, NIV should be used to augment ventilation through the inspiratory assist associated with positive pressure breathing. This inspiratory positive airway pressure (IPAP) not only augments tidal volume but also offloads imposed WOB. NIV also provides a baseline pressure (expiratory positive airway pressure [EPAP] or PEEP) that increases functional residual capacity similarly to CPAP. This lower pressure can improve oxygenation, which makes this mode advantageous when both hypercapnia and hypoxemia are present.

It may be advantageous to start at lower settings and adjust up to achieve desired physiologic goals. These timely changes in settings will probably be necessary to achieve a lower WOB, increase patient comfort, and improve gas exchange. Using protocols, guidelines, or algorithms is extremely useful in NIV and allows for timely and consistent interventions (Figure 3).

Figure 3. NPPV algorithm
Initial pressures of 5 to 10 cm H₂O are commonly used for CPAP. Starting with an FIO₂ of 1.0, CPAP of 8 cm H₂O is often a reasonable first setting. Subsequent adjustments to meet clinical objectives should be made quickly, based on need.

If using a noninvasive ventilator, starting with an IPAP of 8 to 12 cm H₂O and an EPAP of 4 to 5 cm H₂O is reasonable. The difference between IPAP and EPAP on a noninvasive ventilator is equivalent to the level of pressure support being delivered on a conventional ventilator (eg, IPAP 10 cm H₂O/EPAP 5 cm H₂O equals a pressure support level of 5 cm H₂O) (Figure 4). The spontaneous/timed mode available on some noninvasive ventilators allows for a backup rate. This rate can be set based on

Abbreviations: BP, blood pressure; COPD, chronic obstructive pulmonary disease; FIO₂, fraction of inspired oxygen; NPPV, noninvasive positive pressure ventilation; PaCO₂, partial arterial carbon dioxide pressure; PaO₂, partial arterial oxygen pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; RR, respiratory rate; SpO₂, oxygen saturation.
clinician preference in an attempt to ensure minimum minute ventilation. If the patient is breathing above the set rate, the spontaneous breaths suppress the mandatory breaths. Caution should be exercised when using a backup rate on NIV, because a general indication for NIV in acute respiratory failure is that patients must be spontaneously breathing.

**Figure 4.** Examples of ventilator settings

<table>
<thead>
<tr>
<th>A</th>
<th>Example of noninvasive ventilator settings</th>
<th>C</th>
<th>Example of noninvasive ventilator settings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1. PIP = 10 cm H₂O</td>
<td>1. PIP = 10 cm H₂O</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Pressure support level = 5 cm H₂O</td>
<td>2. Pressure support level = 5 cm H₂O</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Example of critical care ventilator settings</td>
<td>D</td>
<td>Example of critical care ventilator settings</td>
</tr>
<tr>
<td></td>
<td>1. PIP = 15 cm H₂O</td>
<td>1. PIP = 18 cm H₂O</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Pressure support level = 10 cm H₂O</td>
<td>2. Pressure support level = 10 cm H₂O</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.


If using a critical care ventilator, a pressure support level of 4 to 7 cm H₂O and a PEEP of 4 to 5 cm H₂O is a common combination to start with. With a critical care ventilator, keep in mind that the pressure support is applied above the baseline pressure (pressure support 10 cm H₂O/PEEP 5 cm H₂O equals a peak inspiratory pressure of 15 cm H₂O) (**Figure 4**). When pressure support is used, there is no backup rate, and the breath cycle criterion is flow (eg, percent of peak inspiratory flow). In the event of apnea, a backup rate is applied in accordance with the machine apnea interval settings. Exercise caution when using a respiratory rate to provide adequate minute volume during NIV in the event of acute respiratory failure.

The FIO₂ setting for NIV should be determined to achieve and maintain the desired oxygenation goal. For example, an FIO₂ of 1.0 may be unnecessary in the absence of hypoxemia. Starting at a lower FIO₂, such as 0.40 to 0.50, is encouraged for COPD patients and acceptable for others as long as the goals are being met. Either way, subsequent adjustments should be made quickly in the acute phase of NIV. Attention should be paid to this element.

Settings such as rise time can be adjusted to meet the needs of the patient. Rise time settings determine how fast the targeted inspiratory pressure is met. This setting
may improve patient-ventilator synchrony, increase comfort, and reduce WOB. In general, rise time should be as fast or as short as possible without creating overshoot on the inspiratory pressure-time scalar. Fast rise times may be useful in the setting of COPD, since they may better offload respiratory muscle work. Other disease processes, such as neuromuscular disease, may require slower rise times.\(^5\) 

Percentage of peak flow cycle should be adjusted on critical care ventilators to improve expiratory synchrony. Clinicians should adjust this setting to ensure that the breath ends as the patient begins to exhale. The patient should not need to use expiratory muscles to force the breath to end. Usually, higher percentage of peak flow settings (40% to 60%) are used for patients with obstructive disorders, while lower percentage of peak flow settings (10% to 25%) are used for patients with low to normal compliance and normal airway resistance.

Attention should be given to setting all alarms. Alarms should correspond with patient parameters and should provide sufficient warning in the event of a large leak, disconnection, apnea, low minute ventilation, high/low tidal volumes, high/low respiratory rate, etc.

Some devices include additional modes for noninvasive ventilatory support. Modes such as average volume-assured pressure support provide predetermined tidal volumes while adjusting inspiratory pressures within a set range, which helps to ensure stable tidal volumes. The theoretical advantage to this type of mode would be to ensure a relatively constant tidal volume in the presence of changing respiratory mechanics. In patients with rapidly worsening respiratory function, this mode may be disadvantageous because of the need for quick ventilator setting adjustments. Proportional pressure ventilation mode enhances the device’s responsiveness to the patient’s breathing effort. This mode is similar to proportional assist ventilation as it may reduce WOB and improve patient-ventilator synchrony. Neurally adjusted ventilatory assist (NAVA) is another mode that may improve patient-ventilator synchrony. In NAVA, the ventilator is triggered by diaphragm electrical activity. This mechanism is not affected by the presence of leaks or mechanical conditions such as intrinsic PEEP. NAVA is currently available only on a critical care ventilator and requires the placement of a specific catheter that detects the diaphragm’s electrical activity. While each of these modes has theoretical advantages, there is no clear evidence that they have any advantage over conventional modes of NIV in acutely ill adult patients.

**Applying the Interface**

Applying the interface to the patient can be challenging. To begin, the patient should be placed in an upright position (head of bed 30 degrees or more). The mask interface should be connected to the circuit, which is attached to a ventilator on initial settings. The mask can be applied to the patient by having either the patient or the clinician hold the mask in place (Figures 5 and 6). Holding the mask in such a manner allows it to be removed immediately for any reason, such as to communicate, and allows the patient to have more control while acclimating to the positive pressure breathing. Either way, the straps should be attached only after the patient has acclimated to the apparatus (Figure 7). Quickly applying the mask and straps should be avoided when possible; this can lead to high patient anxiety and poor compliance.
Figure 5. Patient holding mask

Figure 6. Clinician holding mask

Figure 7. Securing head straps
Adjusting Settings

Once the patient has acclimated and the mask secured, ventilator settings should be adjusted (Figure 8). The main goal of the subsequent adjustments is to achieve normal spontaneous tidal volumes, decrease respiratory distress, improve patient comfort, and normalize arterial blood gases.

Figure 8. Adjusting settings as needed

For hypoxemia, start on 8 cm H₂O with F(IO₂) 1.0, and increase CPAP settings in small increments (2 cm H₂O) until desired goals are reached (eg, Spo₂ > 90%). Once desired goals are reached, adjust F(IO₂) levels as tolerated.

Starting pressures are generally low to allow the patient to become accustomed to the feeling of NIV. It is advisable to adjust pressures in small increments to avoid discomfort. Incremental changes in pressures up or down by 2 cm H₂O are reasonable, with changes being made to meet the patient’s needs. Generally, IPAP is increased until a normal spontaneous tidal volume (5 mL/kg) is achieved. It may
not be possible to know how much support each patient may need; settings are largely dictated by trial and error.\textsuperscript{5}

IPAP/pressure support levels can be manipulated to achieve patient comfort or to maintain an exhaled tidal volume target (5–8 mL/kg/predicted body weight). EPAP/PEEP and Fi\textsubscript{O}\textsubscript{2} settings are titrated to maintain the desired oxygenation goal. EPAP/PEEP settings can also be titrated in 1–2 cm H\textsubscript{2}O increments to improve patient triggering when air trapping is present.

Since gastric opening pressures are 20–25 cm H\textsubscript{2}O, efforts should be made to avoid peak inspiratory pressure greater than 20 cm H\textsubscript{2}O. This should help to minimize gastric insufflation in the great majority of patients.

**Reassessing and Adjusting as Necessary/Recognizing Failure/Weaning**

Due to the severity of illness, assessments/reassessments, and the patient-ventilator interaction, providing NIV is a significant time commitment for the medical team. Critically ill patients requiring NIV should be assessed frequently. Ongoing adjustments should be anticipated during the course of NIV. Adjustments may be necessary per physiologic response and/or patient comfort. If ventilator asynchrony occurs, clinicians should determine the underlying problem and adjust as appropriate. Leaks around the interface can be the source of many problems, such as cycle, trigger, and flow asynchrony, all of which can be remedied with a properly fitted interface.

Cycle asynchrony occurs when the inspiratory phase of the breath will not terminate. In addition to reducing or eliminating leaks around the mask, clinicians can adjust the percentage of peak flow cycle sensitivity or change to a time-cycled mode such as pressure control.

If trigger asynchrony occurs, adjusting trigger sensitivity may be indicated. Trigger sensitivity should be set to be as sensitive as possible without causing auto-triggering. Note that some noninvasive ventilators (eg, Philips Respironics V60) have preset triggering and cycling sensitivity settings that do not require manual adjustment. When air trapping is present, increasing EPAP/PEEP can help offset auto-PEEP and therefore improve patient-ventilator synchronization.

Flow asynchrony can occur with volume ventilation during NIV. Flow-controlled, volume-cycled ventilation is rarely indicated but, when used, changing to a decelerating flow pattern and increasing or decreasing the peak flow rate can help resolve this asynchrony.

Drying of the respiratory system mucosa and secretions may complicate NIV delivery. Active humidification may be considered since NIV involves the delivery of low-humidity gas. Users should be aware that high temperatures associated with active humidification may be uncomfortable for the patient. Low temperatures (30°C, 100% relative humidity) may be adequate. Heat and moisture exchangers are not recommended during NIV.\textsuperscript{2}

The key to recognizing success and failure in NIV is close monitoring. Objective measures such as respiratory rate, heart rate, blood pressure, accessory muscle
use, mental status, and $\text{SpO}_2$ should be monitored continuously. Subjective measures such as patient comfort and dyspnea level should also be assessed. Arterial blood gases should be evaluated within 30 to 60 minutes of NIV initiation to assess oxygenation/ventilation status.

Signs of NIV failure may include hemodynamic instability, deterioration of gas exchange, and mental status changes (increased agitation/decreased consciousness). If any of these signs are present or if the patient’s gas exchange does not improve after one to two hours, endotracheal intubation should be considered.

The most effective method of weaning a patient from NIV is currently unknown. It is reasonable to adjust inspiratory pressures to maintain normal spontaneous tidal volumes (eg, 5 mL/kg/predicted body weight). Inspiratory pressures can also be adjusted to maintain a target respiratory rate (eg, <25 breaths/min). EPAP/PEEP and Fio$_2$ settings may be decreased incrementally to maintain target saturations (eg, > 90%). Keep in mind that some level of EPAP (4 cm H$_2$O) must be maintained to minimize CO$_2$ rebreathing in single-limb circuits. Once minimum settings are reached (eg, IPAP 10 cm H$_2$O/EPAP 5 cm H$_2$O), removal may be attempted. Therapy should be restarted immediately on any sign of clinical deterioration.

If patients have been free of NIV for 24 hours without fatigue or any other signs of clinical decline, the clinician could consider discontinuation of therapy entirely.

**Therapy Location**

Initiation of NIV can occur in multiple areas of the hospital, such as the emergency department, ICUs, and general care wards. The optimal location for management is still controversial. In most cases of NIV in acute respiratory failure, high-level care and monitoring is needed. Emergency departments and ICUs are typically equipped to provide continuous monitoring, skilled clinicians, and access to higher-level care (endotracheal intubation) needed. While it has been shown that NIV can successfully be delivered outside of the aforementioned environments, caution should be taken with any patient receiving NIV outside of these environments. When using NIV on the wards, it may be preferred to have the pH only slightly abnormal (7.30 to 7.35) and to have patients who can tolerate being off NIV for a set amount of time (eg, 30 minutes) before developing respiratory distress. Facilities using NIV outside of an emergency department or ICU may opt to use checklists, advanced training, and enhanced monitoring systems to maximize safety.

**High-Flow Nasal Cannula**

High-flow nasal cannula (HFNC) systems incorporate a flow-metering device and active humidifier capable of providing humidified gas flows up to 60 L/min with an Fio$_2$ ranging from 0.21 to 1.0. Flow rates of 60 L/min should meet or exceed most patients’ inspiratory demands, so that less room air is entrained, resulting in a higher delivered Fio$_2$ compared to standard oxygen delivery devices. These higher flows tend to wash out CO$_2$ from the upper airway, lowering anatomic dead space. Positive expiratory pressure (PEP) may also result, depending on the level of flow used and whether the patient’s mouth is closed. PEP has been shown to increase
end-expiratory lung volume. Providing properly humidified gas enhances comfort and secretion mobilization. All of these potential physiologic benefits help improve ventilation and oxygen while lowering the patient’s WOB. In some disorders, HFNC has been shown to work as well as, if not better than, NIV.

Patients with hypoxemic respiratory failure have been shown to benefit from HFNC therapy. It can be considered a first-line treatment in mild to moderately hypoxemic patients. In this population, we generally recommend starting with a flow of 30 L/min at an FIO₂ of 1.0, then increasing the flow to 50 or 60 L/min if tolerated by the patient. A randomized controlled trial of 310 patients reported a significantly improved 90-day mortality rate in the HFNC group compared to standard oxygen therapy and NIV. The authors believed that this improved mortality may have resulted from a significantly lower intubation rate in patients with a PaO₂/FIO₂ ratio of less than 200 while receiving HFNC compared to the other therapies, although overall intubation rates for this study did not significantly differ. It is thought that the higher delivered FIO₂ and increased PEP may have benefitted these patients. However, clinicians should watch for potential signs of failure, which include lower oxygen saturations, increased respiratory rates, and continued thoracoabdominal asynchrony. Patients exhibiting these signs will most likely require intubation.

Patients with hypercapnic respiratory failure who cannot tolerate NIV masks may benefit from HFNC therapy. Although it does not provide an inspiratory assist to patient efforts, there have been reports of increased tidal volume and exercise capacity in COPD patients. The increased delivered humidity may benefit secretion clearance. The PEP that is created may mimic pursed-lip breathing in this population, alleviating some of the hyperexpansion that may result during an exacerbation. We recommend starting at 30 L/min on an FIO₂ of 0.50 or less to maintain an Spo₂ of 88% to 90%, then increasing the flow in increments of 10 L/min until the observed respiratory distress decreases, a flow of 60 L/min is reached, or the patient cannot tolerate the increase. If the patient’s respiratory distress does not improve within 30 minutes to one hour, NIV should be initiated.

Other patients who may benefit from HFNC therapy include those who are post-extubation, undergoing procedural support of oxygenation, do-not-intubate (DNI) status, and acute heart failure. HFNC therapy may prevent reintubation after extubation. This benefit is thought to be related to the improved oxygenation, reduced respiratory rate, and increased comfort. HFNC therapy can be used to maintain oxygen saturations during intubations. It has also been beneficial in treating hypoxemia and relieving dyspnea in DNI patients with hypoxemic respiratory distress. In acute heart failure patients, HFNC therapy has been reported to improve oxygenation, increase pH, and reduce dyspnea. More research is needed to better understand the application of HFNC therapy in these populations.

**KEY POINTS**

- Noninvasive ventilation (NIV) is used to augment alveolar ventilation, increase lung volume, and unload respiratory muscles in the absence of an endotracheal or tracheostomy tube.
- The primary goals of NIV are to decrease work of breathing, improve gas
exchange, and avoid endotracheal intubation.

- During NIV, positive pressure increases during the inspiratory phase of the breath (inspiratory positive airway pressure/pressure support) and returns to an elevated baseline during exhalation (expiratory positive airway pressure/positive end-expiratory pressure).
- During CPAP, expiratory pressure is elevated above atmospheric pressure. This increases the functional residual capacity (FRC), mean airway pressure, and intrathoracic pressures.
- NIV should be avoided in patients who are apneic or unable to protect their airway from aspiration.
- The use of NIV in the setting of acute cardiogenic pulmonary edema and chronic obstructive pulmonary disease is strongly supported by evidence.
- Clinicians must understand the terminology, mode behavior, and leak compensation capabilities of the ventilator being used to deliver NIV.
- In the acute care setting, oronasal and total face masks are generally recommended. Properly fitted masks maximize patient comfort.
- Clinicians should provide instruction and reassurance for the patient during the initiation of NIV.
- CPAP can be used in the setting of refractory hypoxemia, such as acute cardiogenic pulmonary edema. If hypercapnia is present, NIV should be used.
- If hypercapnia and hypoxemia are both present, NIV can be used since it also provides a baseline pressure that increases FRC similar to CPAP.
- Protocols, guidelines, or algorithms may be useful in guiding the clinical management of NIV.
- Applying the interface to the patient can be difficult. The mask can be held in place to allow the patient to acclimate to the positive pressure.
- Subsequent adjustments immediately after applying the interface will probably be necessary.
- NIV is a significant time commitment for the medical team. Frequent assessment is necessary.
- High-flow nasal cannula should be considered as a first-line treatment in patients with mild to moderate hypoxemia.
- Clinicians should be mindful of skill, monitoring capabilities, and experience levels of the medical team when deciding on when to use NIV.

REFERENCES

7. Gupta D, Nath A, Agarwal R, Behera D. A prospective randomized controlled trial on the
efficacy of noninvasive ventilation in severe acute asthma. *Respir Care.* 2010 May;55(5):536-543.


OBJECTIVES

- To review the physiologic mechanisms behind the use of noninvasive ventilation in critically ill children
- To review the indications for noninvasive ventilation in critically ill children
- To review some of the potential contraindications to noninvasive ventilation in critically ill children

INTRODUCTION

Respiratory failure is the most common type of organ dysfunction and critical illness in children, affecting about half of all patients admitted to pediatric intensive care units (ICUs). Respiratory failure can occur when either or both of the primary functions of the lung (oxygenation and ventilation) are impaired. Hypoxemic respiratory failure, also called type I respiratory failure, occurs when oxygen cannot be adequately provided by the lungs. Type I respiratory failure can be caused by hypoventilation, ventilation/perfusion mismatch, shunt, low inspired oxygen fraction, or, more rarely, impaired diffusion. Hypercapnic respiratory failure, also called type II respiratory failure, occurs when children have impaired ventilation. Type II respiratory failure can be caused by reduced respiratory effort (eg, neuromuscular disease or impaired respiratory drive), increased dead space ventilation (eg, restrictive lung disease, chest wall deformities, or increased airway resistance), or increased carbon dioxide load (eg, fever or increased metabolic demands). Children are more prone to hypercapnic respiratory failure than adults because of their physiologic differences; however, both types of respiratory failure are common in children.

Patients with respiratory failure require mechanical support, either invasively with an endotracheal tube or via a noninvasive interface. Recently, there has been a significant decrease in the frequency of invasive respiratory support. Along with this trend, there has been an increase in the use of noninvasive positive pressure ventilation (NPPV) for the treatment of both acute and chronic respiratory failure. Although the basic principles of noninvasive ventilation have not changed, the associated technology is changing rapidly. The number of masks for noninvasive ventilation for the pediatric population has greatly increased over the past few years. Also, associated management approaches, such as heated high-flow nasal cannula (HFNC), were not in widespread use just a few years ago. It is important that clinicians remain up to date on the current technology and have a firm understanding of the pathophysiology, indications, and contraindications of NPPV.

BRIEF CASE STUDY

A one-month-old, previously healthy girl presents to the emergency department with
a two-day history of cough, rhinorrhea, low-grade fever, and congestion. She has been eating poorly for the past day. Her parents are concerned about her breathing. On examination, she is irritable and cries when examined. She is tachypneic, with a respiratory rate of 80 breaths/min, febrile to 38.3°C (101°F), and desaturated to 88% on room air. Her oxygen saturation improves to 97% with blow-by oxygen. She is mildly tachycardic but otherwise hemodynamically stable. Physical examination is pertinent only for a moderate-to-large amount of nasal congestion. A chest radiograph shows increased bilateral perihilar markings. Capillary blood gas analysis reveals a partial pressure of carbon dioxide of 60 mm Hg with a pH of 7.25. She is diagnosed with acute hypercapnic respiratory failure secondary to bronchiolitis, and the ICU is consulted.

Only a few years ago, this infant might have been intubated and mechanically ventilated in many institutions. However, now there are several noninvasive respiratory support options that can be considered before invasive mechanical ventilation. Additionally, the increased use of these therapies has not been shown to increase duration of illness or the need for emergent intubation in this population.

PATHOPHYSIOLOGY OF NONINVASIVE POSITIVE PRESSURE VENTILATION

By improving gas exchange and respiratory mechanics, NPPV can provide all the salutary effects of invasive mechanical ventilation in patients with acute and chronic respiratory disorders without the potential complications of endotracheal intubation. Noninvasive application of positive end-expiratory pressure (PEEP) improves oxygenation through improved ventilation-perfusion matching resulting from increased functional residual capacity and opening of atelectatic areas of the lung. NPPV can decrease work of breathing by improving pulmonary compliance and counteracting intrinsic PEEP in patients with gas trapping. Meanwhile, noninvasive positive inspiratory pressure augments inspiratory tidal volumes, thereby improving hypoventilation and further reducing work of breathing by unloading the respiratory muscles. By decreasing transmural pressures, NPPV also exerts cardiovascular benefits through decreased left ventricular afterload.

Although the beneficial effects of NPPV can also be seen with invasive ventilation, in contrast, the presence of an endotracheal tube impairs mucus clearance, facilitates entry of microorganisms into the lower respiratory tract, may aggravate bronchospasm, and may cause direct upper airway injury. Furthermore, the procedure of endotracheal intubation itself can be associated with significant adverse events, including hypotension, hypoxemia, bradycardia, and cardiac arrest. Compared to invasive ventilation, NPPV does not interfere with airway defense mechanisms, reduces the need for sedation, and preserves speech and swallowing. The lower potential risk of ventilator-associated pneumonia with NPPV relative to invasive ventilation makes noninvasive support particularly appealing for immunocompromised patients. NPPV also allows greater flexibility in applying and removing ventilatory assistance.

INDICATIONS FOR NONINVASIVE POSITIVE PRESSURE VENTILATION

NPPV has been successfully used in children to treat acute respiratory failure caused by a variety of etiologies. Growing indications for NPPV include the treatment of upper airway obstruction (from a variety of diseases), community-acquired...
pneumonia, status asthmaticus, bronchiolitis, acute respiratory distress syndrome, and acute chest syndrome. Clinicians have also used NPPV as a bridge to unassisted breathing from extubation. However, despite the growing use of this therapy, the published literature consists mostly of surveys, case series, and small cohort studies. Prospective controlled trials in pediatrics that might guide the clinician in determining indications and strategies for using NPPV are lacking.

HIGH-FLOW NASAL CANNULA

Although not traditionally thought of as an NPPV approach, respiratory support through a heated and humidified HFNC is an associated, relatively recent modality that is seeing increased use and success. Providing heated humidified oxygen at flow rates higher than normal spontaneous minute ventilation, HFNC is increasingly being used to support oxygenation and ventilation in critically ill infants, children, adolescents, and adults. A key aspect of these high flow rates is the heating and humidification, which facilitates tolerance to flows above those that can be provided by traditional nasal cannula. The definition of high flow varies based on patient age and weight. In neonates, two to three liters per minute may be considered high flow, while for infants and older children, typically six to 20 liters per minute is considered high flow.

HFNC appears to provide more support to both oxygenation and ventilation than oxygen therapy provided by traditional nasal cannula, but the amount of PEEP provided by this therapy is not entirely clear. One study found that two liters per kilogram per minute of high flow provides at best three to five cm H$_2$O continuous positive airway pressure. Beyond delivering positive airway pressure, HFNC supports respiration and gas exchange by washing CO$_2$ from the upper airway dead space, increasing the delivered inspired fraction of oxygen by matching inspiratory respiratory demand (eg, decreasing entrainment of room air), and promoting mucosal health and improving secretion clearance by providing heated and humidified inspired gas. Overall, HFNC appears to be better tolerated than traditional continuous positive airway pressure therapy in all populations.

Clinicians are increasingly using HFNC to deliver nebulization despite little evidence of its effectiveness. In fact, there is evidence that the delivered dose of nebulized medications is significantly diminished in HFNC, and the decrease is proportional to the increase in flow rate. Further research is needed into this aspect of noninvasive support.

CONTRAINDICATIONS TO NPPV

There are few absolute contraindications to noninvasive respiratory support (Table 1). It should not be applied in patients who have had a respiratory arrest, since more secure airway control and consistent ventilation is generally required in such patients. Facial injuries or malformations that prevent application of a face mask may preclude its use. Similarly, patient intolerance or lack of cooperation unresponsive to “desensitization” or mild sedation may preclude the use of NPPV. Relative contraindications include hemodynamic or other medical instability.

<table>
<thead>
<tr>
<th>TABLE 1. Noninvasive Positive Pressure Ventilation Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
</tr>
</tbody>
</table>


NPPV may increase the risk of aspiration of pooled oral secretions and regurgitated gastric contents. This concern has not been well studied, but prudence suggests that NPPV be used with caution in patients with increased aspiration risk, such as those with an inability to protect the airway, swallowing impairments, and/or copious oral secretions. Concerns that gastric distension from NPPV could lead to anastomotic leakage in patients with recent upper abdominal surgery have not been borne out in two adult studies involving 269 subjects.17

In general, NPPV should be used in centers familiar with its use. Greater clinician experience and expertise with the application of NPPV are associated with higher rates of success.18

COMPLICATIONS OF NONINVASIVE POSITIVE PRESSURE VENTILATION

Adverse effects of NPPV can be categorized as interface related, pressure delivery, and nasopharyngeal symptoms (Table 2). The most common adverse consequences of NPPV are related to poorly fitting masks that can cause skin breakdown and air leaks. Facial skin injury leading to necrosis has been reported in as many as 18% of patients supported with NPPV.19 In patients who require prolonged NPPV for ventilatory support, a rotation of different mask types (as is often standard in the adult population) may decrease the risk for skin breakdown, but obtaining a sufficient choice of interfaces in neonatal and pediatric patients is challenging. Nasal bridge ulceration can also be reduced by using masks with soft silicone seals and lessened strap tension and using artificial skin at the onset of skin reddening (or sooner, prophylactically).

<table>
<thead>
<tr>
<th>TABLE 2. Noninvasive Positive Pressure Ventilation Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interface-related</td>
</tr>
<tr>
<td>Facial skin injury and necrosis</td>
</tr>
<tr>
<td>Air leak</td>
</tr>
<tr>
<td>Eye dryness, irritation, conjunctivitis</td>
</tr>
<tr>
<td>Aspiration of oral secretions</td>
</tr>
</tbody>
</table>
Pressure-related
Patient-ventilator asynchrony
Ear discomfort
Gastric distension
Hyperinflation/autoPEEP
Regurgitation and aspiration
Barotrauma

Air leaks at the skin-mask interface or through the mouth when using a nasal interface may preclude achievement of the prescribed pressures and lead to inadequate treatment. Leaks impact how the NPPV device interprets flow rates, delaying inspiratory or expiratory cycling, and potentially resulting in patient dyssynchrony with the device. Leaks directed toward the eyes are associated with ocular drying and irritation, which can result in conjunctivitis in 16% of patients. Air leaks may also disrupt sleep. The most prevalent nasopharyngeal symptoms, nasal congestion and rhinorrhea, have been attributed to inflammatory mediators and inadequate humidity of inspired gas. These symptoms can be improved with humidification of delivered gas and administration of nasal corticosteroids.

Finally, pressure applied to the upper airway and lungs can result in adverse consequences. Patients may report chest and ear discomfort, as well as exhalation discomfort against high expiratory pressures. Gastric distention is uncommon with pressure support levels lower than 20 cm H₂O, but this complication becomes increasingly prevalent at higher pressures. The risk of necrotizing enterocolitis in premature infants is not increased by the use of NPPV. Barotrauma during NPPV is uncommon, with pneumothorax associated with NPPV occurring in less than 5% of cases. An important issue of concern is the failure to recognize when NPPV fails and continuing to prolong it. Delayed intubation when NPPV has failed to improve a patient’s respiratory status is associated with increased mortality.

Multiple organ failure and pneumonia are the main factors associated with NPPV failure and death in morbidly obese adult patients in hypoxemic respiratory failure. Failure rates of NPPV are as high as 45% to 50% in adults with severe community-acquired pneumonia, especially in those without preexisting cardiac or respiratory disease. It is possible that NPPV failure in these settings could be attributed to insufficient support due to patient-ventilator asynchrony.

INTERFACES
As in adults, the choice of the optimal interface in children during NPPV can play a major role in determining success, failure, and complications. In the past, application of NPPV, particularly in young children, was restricted by the limited number of sufficiently small interfaces. Over the past five years, however, an increasing repertoire of pediatric-sized interfaces has become available, including mouthpieces, nasal masks and pillows, full-face and total face masks, and helmets, although some interfaces are not yet available in the United States. The advantages and disadvantages of each interface type are highlighted in Table 3.
Choice of interface is dependent on both patient and disease characteristics. For example, the helmet has been shown to have a longer inspiratory trigger delay than face masks or endotracheal tubes,\textsuperscript{27} resulting in increased patient-ventilator dyssynchrony and, subsequently, increased patient agitation, higher ventilator settings, and pressure-associated complications during full NPPV support. Conversely, compared to face masks, use of the helmet for CPAP administration in infants with severe bronchiolitis is associated with lower failure rates because of patient intolerance, a reduced need for sedation, and less facial skin injury.\textsuperscript{28} Nasal masks or pillows are often best tolerated by patients due to limited facial coverage, less claustrophobia, and decreased impedance with communication, but they can be uncomfortable in the presence of high nasal resistance. Moreover, nasal masks are inherently associated with more variable pressure delivery due to oral air leaks, and they can induce increased nasal irritation, rhinorrhea, and, less commonly, epistaxis. Full-face or total face masks provide more consistent pressure delivery but also limit oral secretion clearance and increase the risk of aspiration if emesis occurs.

\textbf{KEY POINTS}

- Noninvasive positive pressure ventilation (NPPV) is an increasingly widespread therapy that is being used to treat a wide variety of etiologies of acute and chronic respiratory failure in children.
- Technology is changing rapidly, and clinicians need to be aware of the indications and contraindications for NPPV in children.
- Appropriate patient selection, staff familiarity and comfort with NPPV, and careful monitoring are crucial for its success.
- Children receiving NPPV remain at risk for needing invasive mechanical ventilation, and they require close and frequent monitoring of their respiratory status.

\textbf{REFERENCES}


AIRWAY PROBLEMS OF INTUBATION AND EXTUBATION

Shihab Sugeir, MD, Sameer Kamath, MD, Phillip Lumb, MB, BS, MD, MCCM

Objectives

- Preparation for intubation
- Intubation techniques
- Preparation for extubation
- When to perform a tracheostomy

INTRODUCTION

The ease with which any intensive care unit (ICU) patient can be intubated or extubated varies from relatively easy to extremely difficult, with the potential need for an emergent surgical airway. This chapter will focus on an overall system that can and should be used on every ICU patient. Those patients who are difficult to intubate and extubate will also be discussed.

The Fourth National Audit Project of the Royal College of Anesthetists and the Difficult Airway Society (NAP4) was designed to look at airway complications in the emergency department, the ICU, and during anesthesia. The findings serve as a constant reminder that the ICU is where many airway complications occur and that, when these complications happen, the likelihood of death and neurologic injury is very high.1 Similarly, the National Emergency Airway Registry for Kids (NEAR4KIDS) collaborative was established to better characterize the tracheal intubation (TI) process in the pediatric ICU (PICU). The collaborative has brought to our attention the variability in practice and safety outcomes associated with TI in acutely ill children.2

One of the most stressful situations any physician will face in his/her career is the emergent intubation of a patient in distress. Compounding the stress of the situation is the fact that the clinician is probably the only airway expert in the ICU. However, like most events in the ICU, with proper planning, preparation, and practice, this stressful situation becomes much more manageable with experience. After each successful intubation the focus shifts towards aiding recovery and extubation. A good extubation plan is just as important as one made during intubation, however, the best way to extubate patients has been poorly examined and defined. If intubation was difficult, simply ordering extubation without the presence of appropriate personnel and equipment at the bedside is inappropriate and potentially dangerous.

Occasionally some patients will require prolonged intubation and ultimately may require a tracheostomy to help in the patient’s care and comfort. All of these topics will be discussed in further detail. After finishing this chapter, the intensivist should feel more comfortable with intubation, extubation, and transition to a tracheostomy for patients in the ICU.
BRIEF CASE STUDIES

Adult case study: A 58-year-old, 100-kg woman, who is 160 cm tall with a BMI of 39.1 kg/m², presents with hypoxic respiratory failure secondary to a seasonal influenza infection. Physical examination of the airway is significant for a short neck, a thyromental distance of 2 cm, a small mouth opening, and a Mallampati IV airway evaluation. The decision to intubate is made, and the intubation cart and medications are obtained. The patient is appropriately positioned with the head of bed at 30 degrees and a shoulder roll, putting her into a neck-flexed, head-extended (sniffing) position. The bedside nurse, respiratory therapist, and intensivist are all at the bedside. A time-out is performed to identify the patient, the reason for intubation, and each team member. Preoxygenation is performed with high-flow nasal cannula and transitioned to full face mask with 100% fraction of inspired oxygen (FIO₂). The intensivist then instructs the nurse on the doses of hypnotic and paralytic to administer. Once the patient has been adequately sedated and relaxed, the intensivist uses a videolaryngoscope from the head of the bed to visualize the vocal cords. A grade three view is obtained, and the patient is successfully intubated. The capnograph confirms successful intubation; the confirmation of bilateral breath sounds ensures adequate endotracheal tube (ETT) position. The ETT is then secured, and mechanical ventilation is started. A confirmatory chest radiograph is obtained to ensure that ETT is appropriately positioned.

Over the next several days, the patient begins to have better oxygenation with decreasing FIO₂ requirements. Mechanical ventilation support is weaned until the patient is on spontaneous ventilation with a pressure support of 5 cm H₂O and peak end-expiratory pressure of 5 cm H₂O. A cuff leak is confirmed; the extubation cart, respiratory therapist, nurse, and intensivist are all present at the bedside as the patient is extubated. The patient is placed on humidified face mask and continues to improve over the next several days.

Pediatric case study: A 12-month-old infant boy with DiGeorge syndrome and multiple other medical problems is receiving a blood transfusion on the ward when he develops acute respiratory distress and worsening hypoxemia. A rapid response is called, and the patient is immediately transferred to the PICU on face mask oxygen. He continues to be hypoxemic despite high-flow nasal cannula support. A capillary blood gas analysis reveals mixed respiratory and metabolic acidosis. A decision is made to intubate him to support oxygenation and ventilation. However, the first two attempts (one by a fellow and one by a faculty member) are unsuccessful. The patient is supported with mask ventilation, and the anesthesia service is notified urgently to assist with the intubation. Gastric decompression is achieved using the patient’s G-tube. Direct laryngoscopy by the anesthesia team is unsuccessful, and the patient is not able to be successfully intubated using a videolaryngoscope. A laryngeal mask airway (LMA) is placed and patient supported until TI is achieved using a fiberoptic scope through the LMA by two pediatric anesthesiologists working in tandem. The patient continues to need respiratory support for about 10 days, after which he is weaned from ventilator support and extubated to high-flow nasal cannula. Given the difficulty of establishing his airway, the anesthesia team is notified ahead of time and is immediately available during extubation, with all necessary supplies. A note is made in the electronic medical record about the patient’s difficult airway status to enable providers to prepare adequately in the future.
Several reasons for adverse airway events in the ICU were revealed by the NAP4 audit, including poor identification of at-risk patients, poor or incomplete planning, and a lack of skilled staff and necessary equipment.\(^1\) This review highlights that, in the ICU, a standardized approach must be taken to successfully secure all patients’ airways. In other words, we should treat all patients as difficult intubation patients. Buis et al noted that experience is extremely important. To successfully care for patients with difficult airways, providers must have performed 50 successful endotracheal intubations to have a good success rate.\(^3\)

The pediatric anesthesia literature suggests that children with difficult airways can be reliably identified with a good history and physical examination. The incidence of the unanticipated difficult airway in children is thus very low.\(^4\) As is the case with the NAP4 audit for adults, the NEAR4KIDS collaborative has identified several factors contributing to adverse events (AEs) during TI in critically ill children. Of these factors, only severe hypoxemia (oxygen saturation <80\%) and more than two intubation attempts were statistically associated with AEs.\(^2\)

It should not be a surprise that appropriate planning and preparation are essential for successful intubation. Jaber et al showed that, by using a 10-step bundle, they could lower life-threatening complications such as death, cardiac arrest, severe hypotension, severe hypoxemia, and others, including aspiration, dysrhythmia, and esophageal intubation, significantly. Before using the 10-step bundle, their life-threatening complication rate was 34\%, and other complication rate 21\%. After the 10-step bundle was implemented, life-threatening complications decreased to 21\%, and other complications to 9\%. While they were unable to successfully reduce the life-threatening complication rate and other complication rate to zero, they did make significant improvements in the safety of intubation in the ICU by decreasing the rate of life-threatening complications and other complications by 13\% and 12\%, respectively.\(^5\) The NEAR4KIDS collaborative reported that 19\% of TI episodes were associated with an AE, of which only 3\% were severe.\(^2\) The pediatric critical care community is just starting to measure practice variations and factors contributing to TI-associated AEs in critically ill children. It is hoped that the ongoing NEAR4KIDS initiative will reveal strategies aimed at reducing TI-related AEs in critically ill children.

Once the decision has been made to intubate, the intensivist’s approach to airway examination should be uniform and consistent with every patient, despite the intensivist’s confidence in securing the airway. Using the same technique on all patients ensures that the intensivist is unlikely to encounter unforeseen complications that could have been addressed. The goal of the airway examination is to determine how difficult it will be to safely intubate the patient. With adequate patient cooperation, a thorough airway examination should be performed to the intensivist’s best ability. Some parts of the airway examination can be done very quickly with very little cooperation. Other parts of the examination, that require patient cooperation, may be impossible to complete if the patient is in respiratory distress. Considering this, even in the most emergent of situations, a patient can still be safely intubated even when there is not enough time to perform a brief airway examination (Table 1).

<table>
<thead>
<tr>
<th>TABLE 1. Intubation Protocol</th>
</tr>
</thead>
</table>

225
Pre-intubation
1. Presence of respiratory therapist, bedside nurse, intensivist, and intubation cart
2. Preparation for long-term sedation
3. Time-out performed
4. Preoxygenation for at least three minutes

During intubation
5. Administration of hypnotic and paralytic in rapid-sequence induction technique
6. Application of cricoid pressure
7. Visualization of the glottic opening and intubation

Post-intubation
8. Immediate confirmation with capnography/capnometry
9. Confirmation that there is no mainstem intubation via auscultation
10. Securing endotracheal tube

As previously mentioned, pediatric providers can accurately predict which patients will have a difficult airway. Therefore, knowledge of syndromes and conditions associated with difficult intubation is essential. **Table 2** lists some of the conditions associated with a difficult airway. It should be noted that the pediatric airway has some subtle differences, which is especially true for children younger than age two years. These key differences and their clinical implications are listed in **Table 3**.

<table>
<thead>
<tr>
<th>TABLE 2. Some Conditions Associated with a Difficult Pediatric Airway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty with mouth opening</td>
</tr>
<tr>
<td>Large tongue (macroglossia)</td>
</tr>
<tr>
<td>Micrognathia</td>
</tr>
<tr>
<td>Supraglottic obstruction</td>
</tr>
<tr>
<td>Midface hypoplasia</td>
</tr>
<tr>
<td>Limited neck mobility</td>
</tr>
<tr>
<td>Difficulty with advancing endotracheal tube below the vocal cords</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 3. Differences Between Pediatric and Adult Airways, Including Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Difference</strong></td>
</tr>
<tr>
<td>Dimensions are smaller.</td>
</tr>
<tr>
<td>Head is relatively larger than torso.</td>
</tr>
<tr>
<td>Tongue is relatively larger.</td>
</tr>
<tr>
<td>Epiglottis is large.</td>
</tr>
<tr>
<td>Adenoids and tonsils may be prominent.</td>
</tr>
<tr>
<td>Larynx is more cephalad, with a relatively underdeveloped mandible.</td>
</tr>
<tr>
<td>Vocal cords are angled anteriorly.</td>
</tr>
</tbody>
</table>
endotracheal tube through the cord.

| Airway is narrowest at cricoid cartilage rather than at glottis. | Monitoring cuff pressures and using appropriately sized tubes is critical to prevent subglottic injury. |
| Larynx is funnel shaped versus cylindrical. | Patient should be adequately sedated before attempting airway manipulation. |
| There is a propensity for laryngospasm. |

The external airway examination can be performed when first meeting the patient. Looking at the distance between the thyroid cartilage and the tip of the chin will give the thyromental distance. A thyromental distance of less than seven centimeters, or approximately three fingerbreadths, increases the difficulty of the intubation. Any obvious deviation of the trachea or large neck masses can be quickly elicited by observation or palpation. If the patient is cooperative, ask him/her to extend the head as far back as possible and then return to neutral. The difficulty in tracheal intubation increases with less than 40 degrees of neck extension. Finally, ask the patient to open the mouth with tongue extended, without phonation, to evaluate the Mallampati classification (Figure 1). In addition, the adequacy of mouth opening (inter-incisor distance of >3 cm) suggests feasibility of orotracheal intubation using direct or videolaryngoscopy versus nasotracheal fiberoptic intubation. Neck thickness, compliance of the submental space, and neck mobility should also be assessed.

Figure 1. Airway grade and Mallampati classification

The Mallampati classification is one of the most important examinations in determining the difficulty of safely intubating the airway. The classification ranges in
difficulty from easy to challenging, with numerical denotations of I through IV. Class I airways allow visualization of the entire soft palate, uvula, and tonsillar pillars. Class II airways allow visualization of primarily the soft palate, uvula, and a partial view of the tonsils. Class III includes the soft palate and the base of the uvula. Finally, Class IV allows only the hard palate to be visualized. Classes III and IV are associated with patients who are difficult to intubate. It should be presumed that a patient’s airway will be difficult if an adequate airway examination is unable to be obtained or the patient is unable to cooperate. Mallampati classification is useful in cooperative older children and adolescents. It is often not possible to assess in infants and toddlers.

Once the airway examination has been attempted and/or completed, preoxygenation of the patient should begin. This allows the maximal time before depletion of oxygen reserves, resulting in hypoxemia. Children are more prone to hypoxemia with apnea because of a lower functional residual capacity and higher oxygen consumption. While the tidal volume (indexed to body weight) needed to ventilate may be similar to adults, a higher respiratory rate is needed to achieve adequate carbon dioxide elimination, given higher carbon dioxide production. The pediatric airway is narrower, resulting in more resistance to airflow, as governed by Poiseuille’s law: \[ R = \frac{8\eta l}{\pi r^4} \] (resistance is proportional to the fourth power of the radius). Minimal mucosal edema can severely compromise airflow and ventilation. In terms of preoxygenation techniques, there have been no definitive studies showing superiority of one form over another. However, one form must be chosen and performed. Options include high-flow nasal cannula with potential for \( F_{\text{IO}_2} \) of 100% and some amount of positive end-expiratory pressure, noninvasive positive pressure ventilation using 100% \( F_{\text{IO}_2} \), or the traditional technique of provider-held face mask with 100% \( F_{\text{IO}_2} \), assisting or allowing the patient to breath spontaneously. The authors’ preferred technique is high-flow nasal cannula, because it can be used during both the preoxygenation period and the intubation to allow for apneic oxygenation throughout the entire intubation process.

In conjunction with preoxygenation, patient positioning is paramount to a successful intubation. Proper positioning can be obtained either before or during preoxygenation. The patient should be positioned with the external auditory meatus in horizontal alignment with the suprasternal notch (Figure 2). The neck should be flexed with head extended (sniffing position). Neck flexion and head extension allow for easier mask ventilation should this technique be needed if intubation was unsuccessful on the first attempt. The simplest way of achieving this in the ICU is by placing the back of the bed at 30 degrees and then placing a shoulder roll. In patients with a possible cervical neck injury, care should be taken to avoid further compromise by avoiding placement of a shoulder roll and limiting head extension. While this technique can be successfully adapted for older children and adolescents, in infants and toddlers the best airway alignment is achieved by placing a shoulder roll, which prevents excessive neck flexion caused by a relatively large occiput. Other maneuvers, such as chin lift and jaw thrust, can help tremendously in maintaining airway patency and optimizing conditions before undertaking TI. Patients with limited cervical spine mobility or suspected cervical spine instability should be intubated with another provider maintaining inline traction to prevent inadvertent neck manipulation.

Figure 2. Proper airway positioning
The appropriate sniffing position is shown in C.

Once again, considering the possibility of a difficult airway in all patients, proper positioning is helpful in all scenarios. This is even more pronounced in obese patients. In order to obtain maximal oxygenation and ventilation, clinicians must use positioning to their advantage. By elevating the back of the bed to 30 degrees, gravity offsets the compression of adipose tissue on lung volumes, thereby improving the functional residual lung capacity. Elevation of the bed also decreases the risk of aspiration by keeping the stomach contents distal to the lower esophageal sphincter. The tradition of laying the patient flat should no longer be considered acceptable, especially in obese patients, at any point in the process of securing the airway. This is likely true for patients with acute abdominal distension and acute intra-abdominal pathology, a situation not uncommon in the PICU.

In regard to medications used for obtaining adequate intubating conditions, hypnotics and paralytics are the two categories of medications needed to improve intubating conditions. After preoxygenation, these medications can then be administered. In most cases, the patient will receive both a hypnotic and a paralytic agent. It is beyond the scope of this chapter to go over each medication in detail; however, we will briefly discuss the most broadly used hypnotic and paralytic agents.

There are at least three popular hypnotic agents—ketamine, propofol, and etomidate—that provide adequate intubating conditions. The goal of the hypnotic agent is to provide sedation, relaxation, and amnesia in a hemodynamically stable fashion. The decision as to which medications to use is ultimately at the discretion of the clinician or institution. The authors’ personal preference is to use a one-to-one ratio of propofol to ketamine in a 1.0–1.5 mg/kg dose to provide adequate sedation, amnesia
and relaxation with overall stable hemodynamics. In the brief case study above, the patient would have received 50 mg of ketamine and 50 mg of propofol. Of note, any time a clinician is preparing to intubate a patient, vasoactive agents should be readily accessible in case hypotension results from administration of hypnotic medications. The medications most often used to facilitate TI in children are fentanyl, ketamine, and propofol, with propofol being reserved for hemodynamically stable patients. Infants tend to have heightened vagal tone, and may develop bradycardia with any airway manipulation; therefore, atropine should be immediately available for administration. Code cart and resuscitation equipment should be immediately available, especially when undertaking TI in unstable patients. Transition from negative-pressure to positive-pressure ventilation creates several physiologic derangements in the cardiovascular and respiratory systems that may be poorly tolerated by critically ill unstable patients.

In addition to hypnotics, paralytics should be administered to provide ideal intubating conditions. The two most popular paralytics are succinylcholine and rocuronium. Succinylcholine, 1.5–2.0 mg/kg, or rocuronium, 1.0–1.2 mg/kg, will provide quick and reliable paralysis. Succinylcholine should be avoided in patients with renal failure, burns, crush injuries, and neuromuscular disease. In children, given the possibility of undiagnosed myopathies, succinylcholine carries a black box warning about possible ventricular arrhythmias that can be triggered by its use. Rocuronium is therefore the most commonly used paralytic in the PICU. Some argue that paralytics should not be used until it is clear that ventilation can be achieved; in this case, clinicians may be “burning their bridges.” If a clinician is unable to intubate or ventilate the patient, then the patient will die because the clinician has lost the option of returning to spontaneous ventilation. However, in the ICU, unlike the operating room, patients are intubated for respiratory failure; it is unlikely that patients would be able to adequately ventilate or oxygenate themselves without support.

In contrast to the dogma of maintaining spontaneous ventilation with the avoidance of paralytics, Wilcox et al showed that the administration of neuromuscular blocking agents for emergent tracheal intubation decreased procedure-related complications and hypoxemia. This study included personnel with at least six months of anesthesia training as the initial clinician to secure the airway, with an intensivist available to secure the airway if the trainee was unable to do so. In addition, the study covered multiple settings, including the operating room, ICU, and standard hospital floors. The significant finding of this study was that the use of paralytics resulted in an improved laryngeal view, thereby decreasing complications of intubation. Another source advocating for the use of paralytics to assist in intubation is the guidelines provided by the Difficult Airway Society in 2015. These guidelines specifically state that full neuromuscular block should be used in difficult intubations. Attempts at TI while inadequately relaxed can trigger laryngospasm in pediatric patients, in addition to causing airway injury, making TI more difficult for other clinicians. In patients in whom a difficult airway is suspected, the plan for neuromuscular blockade must be made in conjunction with the pediatric anesthesiologist providing airway backup.

The next physical step to intubating a patient after preoxygenating, positioning, and administering medications is securing the airway with the optimal device for each patient. The decision as to which device to use is usually based on the clinician’s experience with specific devices and the patient scenario. There are a myriad of blades and devices that can be used to secure the airway. What follows is a brief
summary of airway device possibilities. While ETT size tends to be standard in adult patients, in pediatrics, size is determined by the age or weight of the patient (Table 4). Data on safety of cuffed ETTs during the past two decades has resulted in widespread use of cuffed tubes in critically ill infants and children. Cuffed tubes offer several advantages, such as improved airway seal enabling better respiratory support, prevention of macroaspiration, and possible reduction of ventilator-associated infectious complications.

<table>
<thead>
<tr>
<th>Age</th>
<th>Uncuffed ETT</th>
<th>Cuffed ETT</th>
<th>Weight</th>
<th>LMA Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 months</td>
<td>3.5</td>
<td>3.0</td>
<td>&lt;5 kg</td>
<td>1.0</td>
</tr>
<tr>
<td>6 months–1 year</td>
<td>4.0</td>
<td>3.5</td>
<td>5–10 kg</td>
<td>1.5</td>
</tr>
<tr>
<td>1 year–2 years</td>
<td>4.5</td>
<td>4.0</td>
<td>10–20 kg</td>
<td>2.0</td>
</tr>
<tr>
<td>2 years and older</td>
<td>(age in yrs/4) + 4</td>
<td>(age in yrs/4) + 3.5</td>
<td>20–30 kg</td>
<td>2.5</td>
</tr>
<tr>
<td>2 years and older</td>
<td>(age in yrs/4) + 4</td>
<td>(age in yrs/4) + 3.5</td>
<td>30–50 kg</td>
<td>3.0</td>
</tr>
<tr>
<td>2 years and older</td>
<td>(age in yrs/4) + 4</td>
<td>(age in yrs/4) + 3.5</td>
<td>50–70 kg</td>
<td>4.0</td>
</tr>
<tr>
<td>2 years and older</td>
<td>(age in yrs/4) + 4</td>
<td>(age in yrs/4) + 3.5</td>
<td>70–100 kg</td>
<td>5.0</td>
</tr>
<tr>
<td>2 years and older</td>
<td>(age in yrs/4) + 4</td>
<td>(age in yrs/4) + 3.5</td>
<td>&gt;100 kg</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Abbreviation: LMA, laryngeal mask airway.

Most intensivists are familiar with direct laryngoscopy blades, specifically the - Macintosh and Miller blades. Miller blades are generally preferred for infants and toddlers because of their airway characteristics, while all other children are easily intubated using the Macintosh blade of appropriate size. In recent years, videolaryngoscopy has become more prevalent. There is more and more literature showing that it is superior to direct laryngoscopy. Especially in teaching institutions, the videolaryngoscope provides several advantages, one of which is the ability of the supervisor to also visualize the airways as the trainee is operating the device. In the ICU, under the supposition that the airway will be difficult, it seems prudent to use the videolaryngoscope on the first attempt. Recent studies have highlighted the benefits of videolaryngoscopy. A systematic review and meta-analysis by Griesdale et al showed that it improved visualization of the glottis, and, for non-experts, time to intubation was decreased and a higher success rate achieved on the first attempt. Griesdale et al also showed, in a randomized study, that videolaryngoscopy provided a better view of the glottis. Several other studies have also shown that videolaryngoscopy decreases intubation difficulty and improves first attempt success rates. Currently, the particular videolaryngoscope used has little impact on the benefits of videolaryngoscopy in general. It appears that we are in a transition state in which the use of direct laryngoscopy is slowly being supplanted by the superior videolaryngoscope. In contrast, a meta-analysis published in 2014 comparing direct laryngoscopy with videolaryngoscopy in children revealed delayed time to tracheal intubation despite better glottis visualization. This meta-analysis included studies conducted when experience with videolaryngoscopy in children was relatively limited. Over the past few years, interest in videolaryngoscopy has grown with availability of more pediatric-friendly devices and blades. Regular use of videolaryngoscopy for low-risk airways will improve skill and comfort with it. Pediatric intensivists should strongly consider adding it to their mix of skills to enable difficult airway intubations. Most products are comparable. The key is to find a product that a provider or group of providers is most comfortable with, and to stick with it.
In addition to the various laryngoscopes available, having an intubation/airway cart is invaluable. In a situation with limited time and multiple decisions being made simultaneously, things can go wrong despite best efforts. In these times, having adequate resources, including other equipment in the intubation cart, and seeking out additional help can be extremely beneficial. Table 5 lists some suggested contents of an intubation/airway cart. If the provider can visualize the glottic opening, but is unable to pass the ETT through, a smaller tube should be considered. If no visualization is possible, then the Eschmann stylet or fiberoptic scope should be used early on. If the airway still cannot be secured, then preparation for cricothyroidotomy should begin. If help is available from another airway provider, then this person should be sought. Frequent practice and simulation with all the devices, including the cricothyroidotomy kit, is essential. With each attempted intubation, the airway becomes more challenging and the likelihood of significant morbidity and mortality increases.\textsuperscript{13}

<table>
<thead>
<tr>
<th>TABLE 5. Suggested Contents of a Difficult Airway Cart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bag-and-mask ventilation system</td>
</tr>
<tr>
<td>Suction tubing and Yankauer suction equipment</td>
</tr>
<tr>
<td>Nasopharyngeal airway in various sizes</td>
</tr>
<tr>
<td>Oral airway in various sizes</td>
</tr>
<tr>
<td>Direct laryngoscopy blades</td>
</tr>
<tr>
<td>• Macintosh blades</td>
</tr>
<tr>
<td>• Miller blades</td>
</tr>
<tr>
<td>Magill forceps</td>
</tr>
<tr>
<td>Ventilating tube exchange catheters</td>
</tr>
<tr>
<td>Endotracheal tubes in various sizes (cuffed and uncuffed)</td>
</tr>
<tr>
<td>Stylets for endotracheal tubes in various sizes</td>
</tr>
<tr>
<td>Exhaled carbon dioxide detector</td>
</tr>
<tr>
<td>Videolaryngoscope</td>
</tr>
<tr>
<td>Fiberoptic scope</td>
</tr>
<tr>
<td>Eschmann stylet</td>
</tr>
<tr>
<td>Supraglottic airway devices</td>
</tr>
<tr>
<td>Cricothyrotomy kit</td>
</tr>
<tr>
<td>Emergency surgical airway equipment</td>
</tr>
</tbody>
</table>

Some children’s hospitals have successfully created processes to identify and support children with difficult airways during emergencies. Creation of a standardized equipment cart and process of care for children with difficult airways is critical in limiting morbidity and mortality from airway emergencies.\textsuperscript{14} Cricothyroidotomy is challenging in the infant and toddler age groups, and should be considered with caution. A combination of technical difficulty (indistinct anatomic landmarks), small margins of error due to size, and provider inexperience with the procedure can result in serious complications.\textsuperscript{15} Fortunately, in the vast majority of cases, LMAs are able to support patients and also serve as conduits for fiberoptic intubation. However, on the rare occasion cricothyroidotomy becomes necessary, the provider with the most experience with the procedure must perform it while calling for surgical backup.

Once the patient has been successfully intubated, the intensivist’s job is not done. The intensivist must confirm that the ETT has indeed been placed in the trachea and not in the esophagus. The best way to do this is with any form of exhaled carbon dioxide detector, either capnometry or capnography. The benefit of capnography is that an approximation of the partial arterial carbon dioxide pressure can be instantly noted, but both methods are accurate in confirming tracheal intubation. The clinician should then listen to both sides of the chest to ensure that the ETT is not in the right
or left mainstem bronchus. The ETT can then be secured, followed by a chest radiograph if needed to assess tube position and identify any complications that may have occurred from TI.

**Extubation**

The utmost care and attention is required at extubation, especially if intubation was difficult. Special chart and room notifications alerting all providers about the difficulty of intubation is helpful—an approach used at many institutions. While reintubation has been associated with higher mortality in both adults and children, a difficult airway at reintubation has been recently shown to be associated with higher mortality. Identification of readiness to extubate is likely no different in children with a known difficult airway than in the general population. Factors such as adequate muscle strength, ability to support oxygenation and ventilation during a spontaneous breathing trial, presence of a leak around the ETT, wakefulness, and volume/character of secretions should be considered. Unfortunately, there is very little literature to help guide the timing of extubation in a patient who had a difficult intubation.

At the time of extubation, the intubation/airway cart should be brought into the room, and all providers who were present at intubation should be present. The ETT cuff should be deflated and a cuff leak noted. If there is no cuff leak, then extubation may need to be delayed until a cuff leak is present. Airway obstruction is the most common reason for extubation failure in the pediatric literature. Dexamethasone is often administered in preparation for extubation in children without a cuff leak 12 to 24 hours before extubation to reduce presumed mucosal edema. Three to four doses of dexamethasone often suffice for this indication. An aerosol of racemic epinephrine may be administered for those with stridor and signs of acute airway obstruction after extubation. Once a cuff leak is present, events expected as part of the extubation process and future plans should be explained to the patient, which ensures cooperation and optimizes safety. However, this is not possible in young children who have agitation, making assessment of their respiratory status very difficult. Laminar airflow in a calm patient will achieve superior ventilation compared to turbulent airflow present during agitation. Such patients may benefit from a low-dose dexmedetomidine or propofol infusion to maintain a calm and sedate state in the peri-extubation period.

The head of the bed should be elevated to 30 degrees. Suctioning equipment and medications should be available and set up. An airway exchange catheter can be placed through the ETT, taking care to avoid touching the carina. With the airway exchange catheter in place, the ETT should be pulled back above the glottic opening, and the patient should be asked to breathe in and out and even phonate around the airway exchange catheter. If it does not appear that the patient can maintain the respiratory state independently, then, with the airway exchange catheter in place, the patient can be sedated and paralyzed and the ETT repositioned in the trachea under direct vision using a videolaryngoscope or direct laryngoscope. If the patient is able to breathe easily and/or phonate, then the airway exchange catheter and the ETT should be quickly removed from the oropharynx. The patient should be monitored closely for at least 12 hours. All team members should be aware that the patient had a difficult intubation; a review should be made of techniques used for successful intubation. All patients with difficult airways should be extubated during
the day at the beginning of the team’s work schedule to ensure that as much help is available as possible if something happens that requires reintubation. While airway exchange catheters are available for pediatric use, the authors’ experience with them has not been optimal in the very young, for obvious reasons. In older cooperative patients, however, the airway exchange catheters work as well as in adult patients and are very helpful.

**Tracheostomy**

There is still significant debate about when a patient should undergo a tracheostomy. Obviously, patients likely to be extubated within a week of intubation should not undergo a tracheostomy; however, prospective identification of such patients is difficult. The most recent Cochrane review of this topic identified early tracheostomy as on or before day 10 of endotracheal intubation, and late tracheostomy as after 10 days of endotracheal intubation.\(^{18}\) In this analysis, the mortality benefit of early tracheostomy was low (ie, in order to prevent one death, 11 patients needed an early tracheostomy). Other benefits attributed to early tracheostomy (eg, comfort, infection reduction, shorter duration of mechanical ventilation) have been more difficult to demonstrate consistently.

Suitability for extubation should be evaluated daily. If, by day five, the patient is not improving adequately, then preparation should be made for a tracheostomy during the next two to three days. If the patient begins to show improvement, then delaying the tracheostomy is prudent, but not mandatory. At day 10, if the patient will not be extubated, the team should start planning for a tracheostomy.

Pediatric intensivists have a much higher threshold, and rarely consider tracheostomy before three weeks. This explains an almost two- to threefold difference in median times on mechanical ventilation before tracheostomy between children and adults. Determining the right time to perform a tracheostomy in children is a very difficult question to study. Heterogeneity of the patient population, provider biases, institutional biases, and pediatric otolaryngology surgeon availability are some of the factors that play a role. It is nearly impossible to make any meaningful conclusions from published data, given the retrospective nature of published studies. A recent retrospective pediatric study noted a statistically significant reduction in lengths of both ICU stay and hospital stay when tracheostomy was performed within two weeks of needing mechanical ventilator support.\(^{19}\) With an increasing focus on early mobilization, sedation optimization, and delirium prevention in critical care, pediatric intensivists may consider tracheostomies sooner during the next decade. The decision to perform a tracheostomy in a child should be individualized after careful consideration of medical and social factors and weighing the risks and benefits of the procedure. From a technical standpoint, tracheostomy in infants and children in the hands of a pediatric otolaryngology surgeon is safe, with very few surgical complications, and should preferably be performed at centers where one is available.

**Complications of Intubation**

Complications should be anticipated. They can be prevented through standardized preparation and adequate practice. Simulation can play a huge role in improving provider comfort with the physical task of intubation, as well as rehearsing
emergency response for certain commonly witnessed AEs during intubation. Laryngospasm may occur with airway manipulation; the presence of an upper respiratory tract infection predisposes infants to it. This can be overcome using continuous positive airway pressure with the face mask in combination with increasing the depth of sedation. Propofol in small doses can help abort laryngospasm. Rarely, administration of succinylcholine or rocuronium may be needed.

Minor complications such as lip or dental trauma are easily prevented by improved provider vigilance. At no point should any force be needed to successfully pass the ETT through the vocal cords. If any resistance is encountered, the next smaller tube should be passed. Providers using intubating stylets or performing blind nasotracheal intubation should be especially careful to avoid tracheal and/or vocal cord injury. Pediatric airways are more easily injured with forceful intubation attempts and should be handled with care. Tracheal rupture or tears can occur, resulting in pneumomediastinum and subcutaneous emphysema, with devastating consequences. In a Brazilian study, 55% of children had minor airway injury, 24.2% had moderate airway injury, and 10.7% had severe airway injury on bronchoscopy performed after a course of intubation for acute respiratory failure. Moderate lesions identified included vocal cord edema, ulceration of mucosa overlying the arytenoids, posterior glottis ulcerations, vocal cord granulomas, subglottic ulcerations, and cricoid cartilage exposure. Severe lesions included subglottic stenosis, healed fibrous nodules, interarytenoid adhesions, vocal cord paralysis, and posterior subglottic membrane. Although airway lesions related to intubation were well characterized in this study, the short- or long-term consequences of these findings are unknown.20

Subglottic stenosis is a much studied complication in the pediatric literature. Its mechanism is considered to be mucosal necrosis from ischemia related to pressure on the mucosa from the ETT. Careful attention to tube sizing; high-volume, low-pressure cuffed tubes; and improved vigilance toward cuff inflation pressures has markedly reduced the incidence of subglottic stenosis. Consistent use of capnography or capnometry helps with early recognition of esophageal intubation and is the standard of care for confirming tube placement. Right mainstem intubations are not uncommon in neonates and infants, given their size and small margins for error. This is easily identified using auscultation, chest radiography, or bronchoscopy, and should be corrected at the earliest opportunity to prevent total atelectasis of the left lung and barotrauma to the right. Hypoxemia may occur, especially if intubation is not easy and requires more than one attempt. Adequate preoxygenation delays onset of hypoxemia, allowing providers more time to secure the airway. If an airway cannot be secured in a timely manner and hypoxemia is noted, providers should recover saturations with bag and face mask before the next intubation attempt to avoid cardiac compromise from severe hypoxemia.

**SUMMARY**

Proper planning, practice, and preparation are all essential steps in making ICU intubations successful. Many of the patients in the ICU who require intubation will have difficult airways. Treating all patients as if they have a difficult airway is prudent. The intensivist has a lot of autonomy in deciding when and how to intubate the patient, but using a consistent method is beneficial.
The proper positioning of the patient, adequate preoxygenation, use of an intubation cart, and use of paralytics improve intubation success with reduced morbidity and mortality. Patients known to have a difficult airway should be given extra attention at the time of extubation. They should preferably be extubated during the day when additional help is available, with surgical backup if needed. For those patients for whom extubation within ten days is not possible, intensivists should consider the need for a tracheostomy.

**KEY POINTS**

- All intubations in the intensive care unit should be considered difficult.
- The incidence of unanticipated difficult airways is lower in children than in adults.
- Videolaryngoscopy appears to provide a small advantage and should be considered a first-line device. Improving experience with this technology in pediatrics will likely reveal similar results in children in the near future.
- Extubation of a difficult airway should be treated as a new intubation (performed early in the day and with lots of support present).
- Tracheostomy can be performed on or after day 10 with some benefit in adults, and should be considered earlier than what traditionally has been the case in children.

**REFERENCES**


Table of Contents

Mechanical Ventilation: Essentials for Current Adult and Pediatric Practice 2
Copyright 3
Contributors 4
Contents 8
Chapter 1 9
Chapter 2 19
Chapter 3 34
Chapter 4 49
Chapter 5 65
Chapter 6 84
Chapter 7 108
Chapter 8 132
Chapter 9 148
Chapter 10 165
Chapter 11 196
Chapter 12 215
Chapter 13 223